Hemodialysis-induced left ventricular dysfunction

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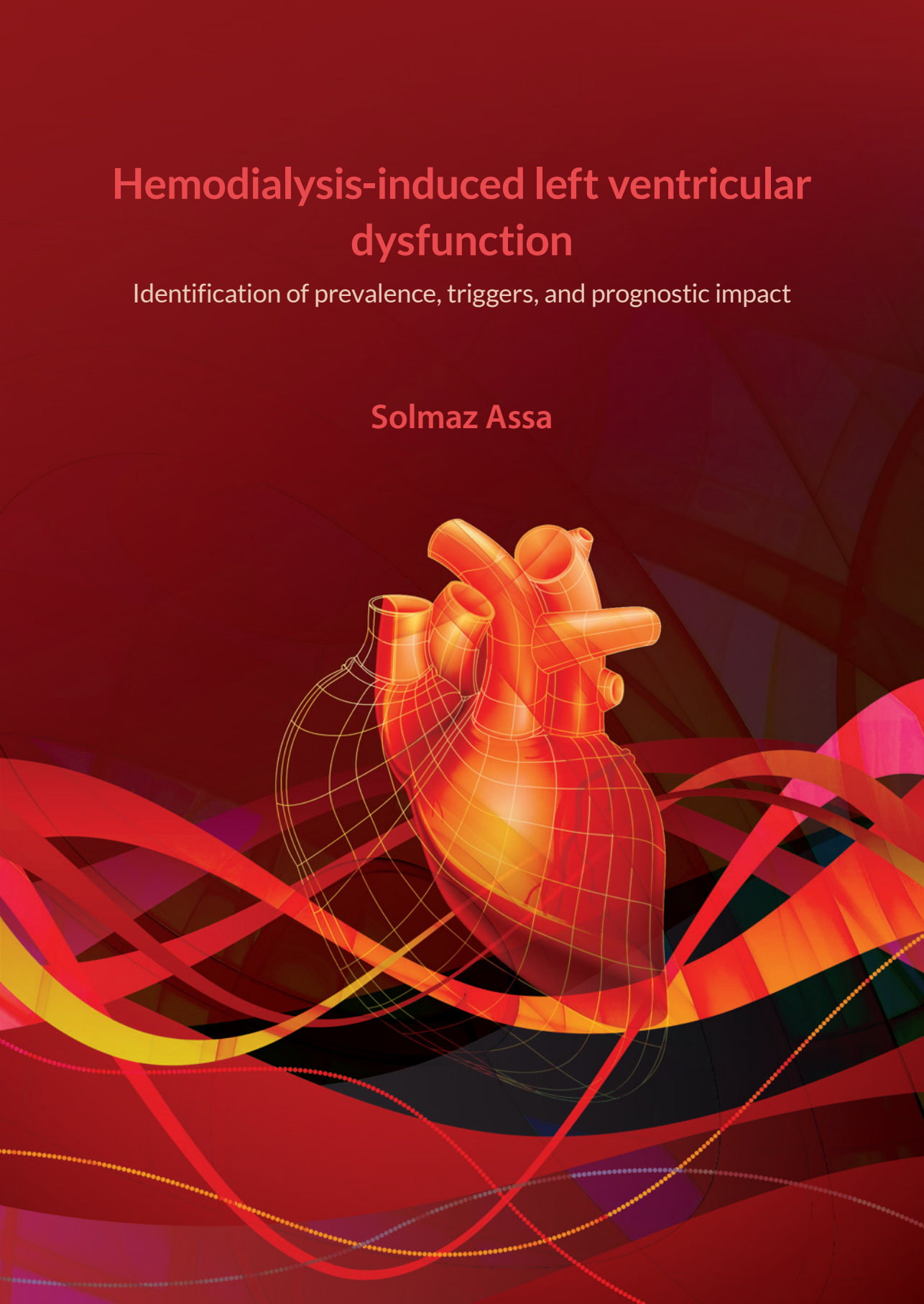
Identification of prevalence, triggers, and prognostic impact

Solmaz Assa



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Chapter 1

Introduction

Hemodialysis-induced left ventricular dysfunction

Hemodialysis is a life-sustaining therapy for an increasing number of patients with end-stage renal disease. Hemodialysis is an intermittent treatment and, worldwide, most patients are treated with a thrice weekly 3 to 4 hour hemodialysis schedule. The intermittent character of the hemodialysis treatment causes large and abrupt fluctuations in hydration status, hemodynamics, and many biochemical parameters.

Hemodialysis patients have a much higher cardiovascular morbidity and mortality as compared with the general population[1,2]. This excess mortality and morbidity is only in part explained by traditional cardiovascular risk factors and pre-existing cardiac disease before the start of dialysis[1]. In addition, recent studies have shown that non-traditional risk factors such as anemia, inflammation, and malnutrition play a deleterious role[3-7]. Although hemodialysis is life-saving by replacement of renal function, it is increasingly recognized that factors unique to the hemodialysis procedure may contribute to the high cardiovascular risk in hemodialysis patients. The specific focus of this thesis is to study the acute effects of hemodialysis on myocardial perfusion and left ventricular function.

Left ventricular systolic function in hemodialysis patients

Left ventricular (LV) systolic dysfunction (abnormal left ventricular contraction) is common among hemodialysis patients. With echocardiography, 15% of patients initiating maintenance dialysis treatment were found to have LV systolic dysfunction[8]. After the start of maintenance hemodialysis, the incidence of systolic heart failure seems to increase[9]. In a prospective cohort study, 90 out of 227 dialysis patients (40%) newly developed systolic heart failure by 1 year after starting dialysis therapy. Improvements in LV systolic function were observed in 46% of patients and these patients had a significantly better cardiovascular outcome than patients in whom LV systolic function remained stable or decreased[10].

A limited number of studies explored the acute effects of hemodialysis on LV systolic dysfunction. We have previously used intradialysis ^{13}N-NH$_3$ positron emission tomography (PET) scanning to quantify changes in myocardial blood flow, LV wall motion, and cardiac output in 7 patients (age 45.0 $\pm$ 18.6 yrs) that were selected for having a low cardiovascular risk[11]. PET scans were performed before hemodialysis and 30 and 220 min after the start of hemodialysis. Ultrafiltration (UF) was only started 30 min after the start of hemodialysis. We observed that myocardial blood flow fell significantly during dialysis (30 min: -13.5 $\pm$ 11.5 %, $p<0.05$; 220 min: -26.6 $\pm$ 13.9%, $p<0.05$). New (not present before hemodialysis) LV hypokinetic/ akinetic regions developed in 2 out of the 7 patients. The fall in myocardial blood flow in segments that developed LV dysfunction was greater than in segments that preserved normal function ($p=0.03$).

Identical results were reported by McIntyre *et al*. Using simultaneous $H_2{}^{15}O$ PET (for myocardial perfusion) and echocardiography (for LV function) in 4 hemodialysis patients (3 of whom had diabetes), this group found that hemodialysis induced in all 4 patients a fall in myocardial blood flow that was of the same magnitude as in our study[12]. Remarkably, all 4 patients developed new regions of LV dysfunction during hemodialysis, again significantly more frequent in those LV segments that experienced the greatest fall in myocardial blood flow.

These observations suggest that hemodialysis induces myocardial ischemia. In patients with coronary artery disease, acute myocardial ischemia rapidly impairs LV contractile function. LV dysfunction can persist some time after the return of normal perfusion. This prolonged LV dysfunction despite the return of normal perfusion is known as myocardial stunning[13]. McIntyre *et al* provided evidence that hemodialysis can indeed induce myocardial stunning by showing that myocardial blood perfusion was restored to pre-hemodialysis levels at 30 min after the hemodialysis session whereas some of the LV regional wall motion abnormalities were still present[12].

According to the Braunwald definition[13], the presence of myocardial stunning can only be proven when information on both perfusion and function is available. However, because of its complexity and costs, $^{13}N\text{-}NH_3$ or $H_2{}^{15}O$ PET scanning is not suitable to screen for hemodialysis-induced reductions in myocardial blood flow and LV dysfunction. Meanwhile, with echocardiography, we can identify patients in whom the reductions in global or regional myocardial blood flow are sufficient to result in reduced LV contraction during hemodialysis.

In the largest study to date, Burton et al studied 70 prevalent hemodialysis patients with pre-, intra- and postdialysis echocardiography and found that 64% of these patients developed significant LV regional wall motion abnormalities (RWMA). RWMA were defined as a reduction in fractional shortening of >20% in 2 or more out of a total of 10 LV regions during hemodialysis[14]. Patients who developed RWMA had a higher mortality during a 1-year follow-up. Patients who developed RWMA during hemodialysis and survived 12 months had significantly lower LV ejection fractions at follow-up echocardiography at 1 year. The same group also studied LV systolic function in pediatric patients aged 2 to 17 years[15]. All but one developed RWMA. This was associated with varying degrees of compensatory hyperkinesis in segments that were not affected. As a result, LV ejection fraction was unchanged. It follows that an unchanged LV ejection fraction does not rule out regional LV systolic dysfunction.

The study of Burton suggests that hemodialysis-induced LV dysfunction occurs in a large proportion of patients. However, these data cannot be simply extrapolated to other hemodialysis populations because of differences in patient and treatment characteristics. It follows that the prevalence and prognostic significance of hemodialysis-induced LV systolic dysfunction in our hemodialysis population is presently unknown. Furthermore, the studies from this group used fractional shortening as the

method to assess (changes in) systolic LV function. This technique is not widely used in clinical practice and does not capture the full complexity of LV contraction mechanics. A number of new echocardiographic methodologies have become available to perform a detailed assessment of different aspects of LV contraction. These include the assessment of regional wall motion abnormalities for each of the 16 segments and the wall motion score index. At present, the prevalence and prognostic significance of hemodialysis-induced LV systolic dysfunction, evaluated by these new methods, is unknown.

Moreover, the pathophysiology of hemodialysis-induced LV systolic dysfunction is unknown. In the study of Burton, age, ultrafiltration-volume, intradialytic hypotension, and higher cTnT levels were independent determinants of the development of RWMA[14]. Interestingly, in our PET study, we found that myocardial perfusion fell already early during hemodialysis (at 30 min) before ultrafiltration was started and the change in myocardial blood flow did not significantly correlate with UF-volume[11]. This lead us to hypothesize that not only UF-induced hypovolemia but also acute dialysis-associated factors are involved in the hemodialysis-induced fall in myocardial perfusion.

Left ventricular diastolic function in hemodialysis patients

Left ventricular diastolic function is associated with myocardial relaxation during diastole and is modulated by myocardial tone[16]. Diastolic LV dysfunction is a frequent finding in dialysis patients. The reported prevalence varies between 25% and 87% depending on definitions used and the patient population that was studied[17-19]. It is generally accepted that diastolic left ventricular dysfunction predisposes to the development of overt heart failure[20]. Like in the non-renal population, diastolic LV dysfunction is associated with an impaired survival in dialysis patients[20].

Previous studies have shown that LV diastolic parameters worsen after dialysis[21,22]. Since atrial pressure is a major determinant of many diastolic parameters like mitral early inflow (E), it is generally assumed that the dialysis-induced hypovolemia is the main reason for worsening of diastolic parameters during dialysis. This pre-load dependence of conventional diastolic parameters has been largely overcome by tissue velocity imaging (TVI). This technique directly measures the velocity of the relaxation of cardiac tissue instead of the blood flow through the mitral valve. Although tissue velocity imaging seems to be less load dependent, some studies demonstrated that LV diastolic function measured by tissue velocity imaging deteriorated from pre- to postdialysis and this observation was even used as an argument for the volume dependency of tissue velocity imaging[23-25]. However, to date no study has evaluated LV diastolic function during dialysis and changes in diastolic function have not been studied in association with volume parameters. Therefore, the exact interaction between volume changes during dialysis and the change in diastolic parameters remains to be elucidated.

Possible mechanisms of hemodialysis-induced LV dysfunction

Various factors render hemodialysis patients sensitive for the development of myocardial dysfunction during dialysis. These include structural vascular disease, inflammation, endothelial dysfunction, and various specific hemodialysis-related factors.

Structural macro- and micro-vascular disease

Uremic patients have a high prevalence of coronary atherosclerotic lesions[1,26] and structural and functional alterations in the microcirculation[27,28]. Specifically, a reduction in capillary density ('myocyte-capillary mismatch') has been described[27,28], which is, in part, explained by left ventricular hypertrophy. Left ventricular hypertrophy also renders the ventricle more sensitive to acute changes in filling pressure as occurs during UF-induced hypovolemia[29]. Increased peripheral arterial stiffness has an adverse effect on the regulation of myocardial blood flow and reduces the ischemic threshold[30]. Left ventricular hypertrophy together with increased vascular stiffness leads to a propensity to reduced subendocardial blood flow[31].

Endothelial dysfunction

Myocardial perfusion reserve has been found to be decreased in patients with chronic kidney disease[32], in diabetic hemodialysis patients[33] and in young adults after renal transplantation[34] in the absence of coronary artery disease. This indicates that reduced renal function is associated with attenuated coronary vasodilator capacity even in patients without obstructive coronary disease[32]. This disturbed coronary vasodilator capacity has been linked to endothelial dysfunction that can be found in most hemodialysis patients. Myocardial blood flow is predominantly regulated by local arterial and arteriolar vasodilatation in response to increased demand. Various systems/substances play a role in this complex regulatory process, including nitric oxide, prostacyclin, endothelin, adenosine, serotonin and the autonomic system. It follows that adequate endothelial function is crucial for the regulation of myocardial blood flow under circumstances of hemodynamic stress like ultrafiltration-induced hypovolemia.

Chronic systemic inflammation

As much as 35 to 60% of hemodialysis patients have signs of inflammation as reflected by increases of proinflammatory cytokines or acute phase proteins[35]. Levels of most circulating proinflammatory cytokines are much higher in hemodialysis patients than in normal controls[36]. Elevated levels of inflammatory factors are associated with an increased risk of cardiovascular mortality and morbidity in dialysis patients[5-7, 37]. Iseki *et al* showed that hemodialysis patients with CRP levels >10 mg/L had a 3.5-times higher mortality risk at 5 yr of follow-up[38]. In another study, dialysis

patients with CRP levels >8 mg/L had a nearly two-fold higher mortality risk[39]. Not only CRP but also higher levels of other inflammatory markers such as IL-6[40], IL-18[41], TNF-α[36], leukocytes[42], fibrinogen[43], hyaluronan[44], myeloperoxidase[45] and pentraxin-3[46] and lower levels of serum albumin[47] are associated with cardiovascular morbidity and mortality in uremic patients. There is a strong link between inflammation, malnutrition, and accelerated arteriosclerosis[6]. A recent study showed that patients with hemodialysis-induced myocardial stunning have higher levels of circulating endotoxin levels which is associated with higher CRP levels[48]. At present, the origin of the inflammation is unknown but the hemodialysis procedure itself may be involved.

Hemodialysis-specific factors

Hemodialysis induces changes in hemodynamics and shifts in electrolytes and pH, and is associated with close contact of blood with the extra-corporal system. All of these can be assumed to be able to affect myocardial blood flow, and thus LV function.

UF-induced hypovolemia

During hemodialysis with ultrafiltration, blood volume decreases due to an imbalance between the ultrafiltration-rate and the plasma refilling rate[49,50]. The hypovolemia elicits cardiovascular compensatory mechanisms to maintain an acceptable blood pressure. Since many hemodialysis patients have inadequate compensatory function it is not surprising that hypotension is one of the most frequent complications of hemodialysis[49]. It is likely that hypovolemia-associated reductions in blood pressure during hemodialysis may compromise myocardial blood flow. A stable blood pressure, however, does not exclude a role for hypovolemia in the fall in myocardial blood flow. Hemodialysis with UF is associated with a significant reduction in cardiac output that does not necessarily lead to hypotension due to an increase in peripheral vascular resistance[51-53]. The fall in cardiac output may compromise myocardial blood flow and, in combination with increased afterload, negatively influence the balance between oxygen supply and demand. However, the results from our recent study suggest that, besides UF-induced hypovolemia, other mechanisms are involved as we observed that myocardial blood flow fell already significantly within 30 min after the start of hemodialysis without significant ultrafiltration[11].

Hemodialysis-associated electrolyte shifts

Many electrolyte shifts occur during hemodialysis. In particular, hemodialysis induces rapid reductions in potassium levels[54]. These changes in potassium levels are believed to play a key role in the development of fatal and nonfatal cardiac rhythm disturbances in hemodialysis patients[55-57]. Calcium levels may rise, fall, or remain stable during hemodialysis depending on the dialysate calcium concentration[58]. The

use of relatively low calcium dialysate levels (1.25 mmol/l) is associated with reduced myocardial contractility, blood pressure[58,59] and arterial compliance[60,61] as well as with cardiac arrhythmias[61,62] compared with higher calcium dialysate concentration (1.75 mmol/l). Hemodialysis induces modest reductions in magnesium levels, and lower magnesium levels are suggested to be associated with lower intradialysis blood pressure[63]. Plasma sodium levels may rise in those patients that start hemodialysis with decreased sodium levels and are dialysed with a regular dialysate sodium concentration (138-140 mmol/l). The effect of such an increase in sodium levels on the heart is currently unknown. Hemodialysis also induces a rapid increase in bicarbonate levels (and pH) as a result of overcorrection of the metabolic acidosis. A high bicarbonate concentration may negatively affect cardiac function[64, 65].

Hemodialysis-associated bioincompatibility reactions

Hemodialysis is capable of inducing various inflammatory pathways, mainly as a result of contact between the blood and the extra-corporal system. Leukocyte activation is predominantly mediated by alternative route complement system activation and leukocyte degranulation by direct membrane contact and heparin[66]. Leukocyte activation is also evidenced by increased leukocyte transcript levels of several pro-inflammatory cytokines such as TNF-alpha and Il-8[67]. Leukocyte activation results in an early (nadir after ±15 min) granulocytopenia due to sequestration in (mainly) the pulmonary vasculature which coincides with a transient drop in arterial blood PO_2[66,68]. Leukocyte degranulation leads to increases in plasma levels of degranulation products such as myeloperoxidase[66]. This is one of the mechanisms by which hemodialysis acutely induces oxidative stress. Data in hemodialysis patients are limited but a recent study has shown that hemodialysis indeed induces increased leukocyte transcript levels of several pro-inflammatory cytokines such as TNF-alpha and Il-8 in a proportion of patients[67]. Although polysulfon dialysers are considered biocompatible, they can activate complement[69,70] and leukocytes[67,71], and induce a fall in arterial $P0_2$[69,70].

The concept that the hemodialysis procedure as such can induce an inflammatory response that has prognostic importance is not new. A Dutch study showed that a rise in CRP during hemodialysis was associated with a higher mortality rate[72]. Notably, the CRP rise was specifically related to the hemodialysis procedure itself. In this study, a rise in CRP levels during hemodialysis occurred in the same frequency in cellulose-based and synthetic polymer dialysers[72].

Hemodialysis-associated bioincompatibility is a potential, but hypothetical, factor explaining the fall in myocardial blood flow. The time course of the hemo-dialysis-associated bio-incompatibility reaction has similarities with the kinetics of the hemodialysis-induced fall in myocardial blood flow. Both occur early, within 30 min after the start of hemodialysis. Bioincompatibility reactions have also been shown to

be capable of inducing significant alterations of the circulation (pulmonary vasoconstriction, an increase in peripheral vascular resistance, and reductions in cardiac output and arterial blood pressure) in an animal model[73]. Recently it has become clear that temporary myocardial dysfunction secondary to sepsis or burns is mediated by complement activation of C5a receptors on cardiomyocytes[73,74]. Likewise, complement activation in the extracorporeal circuit may negatively affect cardiac function during hemodialysis. Alternatively, activated neutrophils and monocytes may release TNF-alpha and other pro-inflammatory cytokines that have a cardiodepressive effect.

Prognostic significance of hemodialysis-induced LV dysfunction

Preliminary data suggest that hemodialysis-associated LV dysfunction is associated with a worse outcome[14]. Repetitive hemodialysis-induced reductions in myocardial blood flow and myocardial ischemia might well be a pathogenetic factor in the high cardiovascular morbidity and mortality in hemodialysis patients. Myocardial hypoperfusion may trigger arrhythmias[2] and repetitive hemodialysis-induced myocardial ischemia may have a role in the development of heart failure[75-77], a highly prevalent condition in hemodialysis patients[9].

Aims and outline of this thesis

The major aims of this study are:

1. To establish the prevalence and the prognostic impact of hemodialysis-induced LV dysfunction.
2. To elucidate mechanisms or pathways that are pathophysiologically involved in hemodialysis-induced LV dysfunction.

In *Chapter 2,* we present a case showing that hemodialysis is capable of inducing myocardial ischemia that differed from that induced by adenosine, the routinely used stressor for ischemia testing.

In *Chapter 3,* we studied whether intradialysis rises in cTnI levels as a sensitive biomarker reflecting myocardial ischemia during hemodialysis are associated with all-cause mortality and cardiovascular outcome.

In *Chapter 4,* we explored the acute effects of hemodialysis on global and regional LV systolic function by serial echocardiography before, during, and after dialysis. In addition, we studied the association between hemodialysis-induced LV systolic dysfunction and patient and dialysis-related factors as possible underlying mechanisms and its impact on mortality outcome.

As mentioned above, no study has evaluated diastolic function parameters during hemodialysis. In *Chapter 5* we studied the acute effects of hemodialysis on diastolic function using serial echocardiographic assessments in relation to the changes in blood volume.

In *Chapter 6* we explored whether systemic inflammation and endothelial dysfunction are involved in the pathophysiology of hemodialysis-induced LV systolic dysfunction. The first objective of this study was to evaluate whether patients with hemodialysis-induced LV systolic dysfunction have elevated predialysis plasma levels of markers of inflammation and endothelial injury. The second objective was to investigate whether patients with hemodialysis-induced LV systolic dysfunction have an exaggerated bioincompatibility response to hemodialysis as a potential source of systemic inflammation.

Myocardial systolic dysfunction has deleterious effects on development of cardiac failure and eventually cardiovascular mortality. However, the contribution of acute LV systolic dysfunction during hemodialysis to the progression of cardiac dysfunction and cardiovascular mortality over time is still largely unknown. In *Chapter 7*, we evaluated the association between hemodialysis-induced LV systolic dysfunction and mortality and cardiovascular events during two years follow-up as primary outcome and the evolution of LV systolic and diastolic function during a one-year follow-up, as the secondary outcome.

In *Chapter 8,* we discuss the main results of the studies presented in this thesis and translate these findings into recommendations for future research.

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Chapter 2

Comparison of Cardiac Positron Emission Tomography Perfusion Defects During Stress Induced by Hemodialysis Versus Adenosine

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Abstract

The cardiac stress imposed by hemodialysis may differ from that induced by pharmacologic agents used for myocardial perfusion imaging-based stress testing. With repetitive intradialytic ^{13}N-NH_3 positron emission tomography, we showed that standard hemodialysis had an acute adverse effect on cardiac perfusion and left ventricular function that was not detected by standard diagnostic adenosine stress testing.

Introduction

Cardiac ischemia is a frequently missed diagnosis in hemodialysis patients. This leads to insufficient treatment and may contribute to the elevated cardiac mortality rate in dialysis patients[1]. The underdiagnosis is explained largely by differences in presentation of cardiac ischemia between dialysis and nondialysis patients; for example, chest pain is absent in most dialysis patients with acute myocardial infarction and ST elevation occurs much less frequently in comparison with nondialysis patients[1]. Recognizing cardiac ischemia in dialysis patients is hampered further by the lower diagnostic accuracy of cardiac troponins and noninvasive ischemia testing in this group compared with nondialysis patients. Although hemodialysis is life-saving, it is recognized increasingly that hemodialysis as such may have acute adverse effects on the heart[2-4]. The cardiac stress imposed by hemodialysis may differ from that induced by pharmacologic agents used for myocardial perfusion imaging–based stress testing. This may explain in part the contrast between the elevated cardiac ischemic event rate and lower diagnostic accuracy of cardiac ischemia testing in dialysis patients. We show that hemodialysis is capable of inducing myocardial ischemia that was not diagnosed with routine ischemia testing using adenosine stress positron emission tomography (PET) detection of ammonia labelled with ^{13}N-NH$_3$ on a nondialysis day.

Case report:

A 60-year-old nondiabetic male dialysis patient with an uneventful cardiac history participated in a study of the effect of hemodialysis on myocardial blood flow and left ventricular function[3]. The underlying cause of his kidney failure was hypertensive kidney disease and he had been receiving hemodialysis for 6 years. A predialysis echocardiogram showed left ventricular hypertrophy, diastolic dysfunction (E/A ratio, 0.51), and normal left ventricular ejection fraction. The hemodialysis session (duration, 4 hours; ultrafiltration volume, 3,750 mL) was clinically uneventful, and blood pressure gradually decreased from 145/80 mm Hg at the start of hemodialysis to a nadir of 125/80 mm Hg at the end of the dialysis session. Myocardial blood flow and left ventricular function were assessed by gated ^{13}N-NH$_3$ PET before dialysis and at 30 and 220 minutes of hemodialysis. Global myocardial blood flow decreased by 26% at 30 minutes of dialysis and by 44% at 220 minutes of dialysis compared with baseline (Fig 1A). New left ventricular regional wall motion abnormalities, which were absent at baseline (Movie S1, available as online supplementary material), were observed in 2 of 17 left ventricular segments at 30 minutes of dialysis and 8 of 17 left ventricular segments (anterior, septal, and inferior regions) at 220 minutes of dialysis,

resulting in impaired left ventricular contraction (Movie S2). The decrease in myocardial blood flow was of a significantly larger magnitude in segments that developed regional wall motion abnormalities than in those with preserved function (-47%±6% vs -33%±3%; P=0.004). Because intradialytic PET is not a standard diagnostic test for myocardial ischemia, the patient subsequently underwent a gated adenosine stress ^{13}N-NH$_3$ PET study on a nondialysis day 2 weeks later while on the same medication. This study yielded no signs of myocardial ischemia (Fig 1B) and intact myocardial perfusion reserve (ratio, 2.1; normal, >2), but showed an increase in left ventricular diameter during adenosine stress, suggesting transient ischemic dilatation (ratio of left ventricular volume poststress versus at rest, 1.15; abnormal>1.20). Although the adenosine stress ^{13}N-NH$_3$ PET findings were not strongly suggestive of coronary artery disease, the studies performed under dialysis stress were of concern; therefore, the patient underwent coronary angiography. The results (Movies S3 and S4) showed severe calcifications in the left and right coronary arteries, with significant stenosis in the midsection of the right coronary artery, which was treated with a stent.

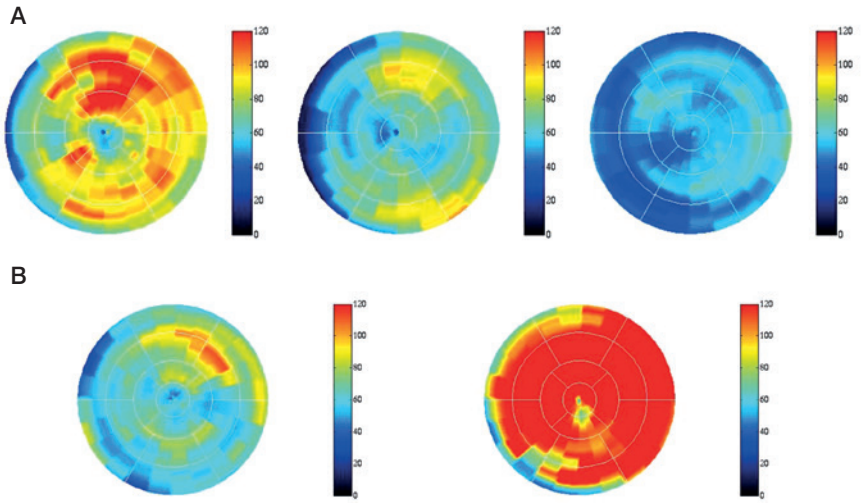

Figure 1 Polarmap reconstruction of [13N]ammonia PET scans.

The polarmap is divided into 17 segments. Scaling bars show reference values for myocardial perfusion (in mL/min/100 g of myocardial tissue), with red indicating high and dark blue indicating low myocardial perfusion. (A) Scans before (left panel) and at 30 (middle panel) and 220 minutes (right panel) of hemodialysis. Myocardial perfusion is severely decreased at 220 minutes of hemodialysis (right panel). (B) Scans of a nondialysis day at rest (left panel) and during intravenous adenosine administration (right panel). Myocardial perfusion is increased during adenosine stress (right panel).

Discussion

Remarkably, the diagnostic adenosine stress-gated ^{13}N-NH_3 PET study did not unequivocally indicate myocardial ischemia, whereas the intradialytic gated ^{13}N-NH_3 PET showed an impressive decrease in myocardial blood flow and left ventricular function. There may be 2 possible explanations for this difference. First, the pharmacologic agents used for myocardial perfusion imaging–based stress testing, such as adenosine, may exert less cardiac stress in dialysis patients compared with nondialysis patients, for example, due to impaired cardiac autonomic function and resulting in a blunted vasodilatory and heart rate response[5]. This factor also may, at least in part, explain the lower diagnostic sensitivity of myocardial perfusion imaging–based stress testing in dialysis patients compared with nondialysis patients. Second, the cardiac stress induced by hemodialysis may be greater than the stress induced by adenosine. It is evident that hemodialysis is stressful for the cardiovascular system because hemodynamic instability is one of its most frequent complications and the risk of sudden death is linked temporally to the hemodialysis procedure[6]. During hemodialysis, ultrafiltration induced hypovolemia elicits an increase in peripheral systemic resistance, resulting in increased afterload for the heart. Particularly in combination with coronary arteriosclerotic lesions, these hemodynamic changes may negatively influence the balance between oxygen supply and demand and predispose to myocardial ischemia. Additionally, the microcirculatory regulation of myocardial blood flow may be impaired in dialysis patients and may deteriorate further during hemodialysis as a result of electrolyte and/or acid-base shifts or systemic inflammatory response due to the interaction between blood and the extracorporeal system.

In this patient, the area of hypokinesia that developed during dialysis (anterior, septal, and inferior regions) corresponded only partly to the site of significant stenosis. This may be due to diffuse coronary artery sclerosis in this patient. Alternatively, microcirculatory disease may have contributed to the development of a larger area of hypoperfusion than expected on the basis of the coronary lesions. McIntyre et al[2] have shown that hemodialysis may induce segmental myocardial hypoperfusion with matching left ventricular systolic dysfunction even in the absence of significant coronary lesions. In conclusion, in this patient, hemodialysis had acute adverse effects on cardiac perfusion and left ventricular function that were not detected by standard diagnostic adenosine stress testing.

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Chapter 3

Determinants and Prognostic Significance of An Intradialysis Rise of Cardiac Troponin I Measured by Sensitive Assay in Hemodialysis Patients

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Abstract

Background Previous studies using conventional cTnI assays reported conflicting results on the evolution of cTnI levels during hemodialysis. The determinants and prognostic significance of changes in cTnI during hemodialysis are presently unknown. The aim of this prospective study was to characterize the determinants and prognostic significance of intradialysis changes in cTnI using a sensitive assay.

Methods cTnI was measured before and after hemodialysis with a sensitive assay in 90 chronic patients without acute cardiac symptoms. Multivariable regression analyses were used to identify factors that were associated with intradialysis rise in cTnI. The prognostic effect of an intradialysis rise in cTnI during a 52-month follow-up was evaluated using Cox regression models. The primary and secondary endpoint was the incidence of major adverse cardiovascular events and all-cause mortality, respectively.

Results Predialysis cTnI was elevated in 31 patients (34 %). cTnI increased significantly during dialysis and this had a trend to be associated with longer dialysis vintage. A greater intradialysis rise in cTnI was associated with a significantly higher incidence of cardiovascular events, also after correction for age, gender, dialysis vintage, residual diuresis, previous cardiovascular events, and predialysis cTnI levels (HR per 10 ng/L rise in cTnI: 1.21; CI 1.06–1.38; p 0.005).

Conclusion TnI levels rise significantly during hemodialysis and a greater intradialysis rise in cTnI is associated with an increased incidence of cardiovascular events. These findings suggest that hemodialysis has an acute deleterious effect on the heart. An intradialysis rise in cTnI may help identify patients who are susceptible to the hemodynamic stress of hemodialysis.

Introduction

Plasma levels of cardiac troponins are often elevated in hemodialysis patients without clinical evidence of acute myocardial damage[1-3]. This limits the diagnostic use of cardiac troponins in suspected acute coronary syndromes in dialysis patients. At the same time, elevated predialysis cardiac troponin levels are associated with an adverse longterm outcome[4,5]. Consequently, the interest in cardiac troponins in dialysis patients has shifted from a diagnostic use in suspected coronary syndromes toward the use for risk stratification.

In previous studies, using conventional assays for detection of cTnI, the prevalence of elevated cTnI levels in dialysis patients has been reported to vary between 5 and 18 %, which is much lower than the 30–85 % that has been reported for cardiac troponin T[4]. However, using a sensitive assay, a recent study showed that elevated predialysis cTnI levels were present in up to 51 % of asymptomatic hemodialysis patients[6]. Furthermore, the same group showed that elevated predialysis cTnI levels were associated with an increased incidence of cardiac events during follow-up[6]. The mechanism why cTnI levels are elevated in hemodialysis patients is presently not clear but it may well be related to the hemodialysis procedure itself since several groups have reported that hemodialysis may induce a reduction in myocardial perfusion and elicit regional wall motion abnormalities[7,8]. Identification of the determinants of intradialysis rises in cTnI may help elucidating the pathophysiological mechanism of elevated troponins in this patient group. Previous studies using conventional cTnI assays have reported conflicting results on the change in cTnI levels during hemodialysis with some studies reporting no change[9-11] and others a decrease in cTnI levels[3,12]. The change in cTnI levels during hemodialysis has thus far not been studied by sensitive assays. In addition, the prognostic significance of intradialysis changes in cTnI levels has not been studied. The aim of this prospective study was, therefore, to characterize the determinants and assess the prognostic significance of intradialysis changes in cTnI using a sensitive assay.

Subjects and Methods

Patients

Adult (≥18 years) patients of our Dialysis Center who were on maintenance hemodialysis for more than 3 months and gave informed consent were eligible for this study. Patients with recent (3 months) acute myocardial infarction, patients with heart failure NYHA class 3 and 4, and hospitalized patients were excluded. The inclusion of patients occurred at July 2006. The study was performed according to the principles of the declaration of Helsinki.

Dialysis procedure

All patients were dialyzed three times a week for 4 h using a low-flux polysulfone hollow-fiber dialyser (F8, Fresenius Medical Care, Bad Hamburg, Germany). Blood and dialysate flow rates were 250–350 and 500 mL/min, respectively. Patients were dialyzed with bicarbonate-buffered dialysate using constant dialysate sodium conductivity (13.9 mS/cm) and a linear ultrafiltration rate. Dialysate temperature was 36.0 or 36.5° C.

Laboratory procedures

Blood samples were collected before (predialysis) and at the end (postdialysis) of the first dialysis session of the week. Samples were centrifuged within 30 min of collection at 3,500 rpm for 15 min. Next, the supernatant was stored at -80° C until measurement. Prior to assay, samples were thawed and re-centrifuged. The samples were analyzed at a single time point to eliminate inter-assay variability. Laboratory personnel performing the assays were unaware of patient data or outcome.

cTnI was measured with the ARCHITECT STAT assay, a chemiluminescence microparticle immunoassay (CMIA). This sensitive assay has a limit of detection of 10 ng/L and a coefficient of variation of <10 % at 32 ng/L. The 99th percentile cut-off in a normal reference population was previously established at 28 ng/L[13,14]. A cTnI level <28 ng/L was considered normal.

The following clinical data were collected at the time of blood sampling: primary kidney disease (according to codes of the European Renal Association, European Dialysis and Transplantation Association), co-morbidity, predialysis systolic and diastolic blood pressure, electrocardiography (EKG), ultrafiltration volume, and medication use. Left ventricular hypertrophy (LVH) was electrocardiographically defined by the Sokolow–Lyon voltage criteria[15]. Hypertension was defined as either the use of anti-hypertensive drugs or a predialysis blood pressure >140/90 mmHg. Diabetes mellitus was defined as fasting blood glucose level >126 mg/dL (7.0 mmol/L) or treatment with insulin or oral anti-diabetic agents.

Definition of study endpoints

The primary endpoint in this study was the occurrence of major cardiovascular events (MACE). The secondary endpoint was all-cause mortality. Patients were analyzed at baseline for a history of and prospectively followed for a maximum of 52 months for the occurrence of MACE, which was defined as cardiac, cerebrovascular, or peripheral vascular events. Cardiac events were defined as acute myocardial infarction, newly observed unstable angina pectoris, requirement for coronary bypass surgery or angioplasty, or sudden cardiac death. Acute myocardial infarction was diagnosed if at least two of the three following criteria were fulfilled: clinical status, elevated heart enzymes, and EKG changes. Cerebrovascular events were defined as

stroke, ischemic insults, or newly diagnosed >70 % stenosis of the extracranial carotid artery. Strokes and ischemic insults had to be verified by CT or MRI. Peripheral vascular disease was defined as intermittent claudication with angiographically or sonographically proven stenosis >50 % of the major arteries of the lower limbs or ulcers caused by atherosclerotic stenosis or surgery for this disorder. These data were clinically driven and were reported by physicians which were blinded to the cTnI results.

Statistical analysis

Normally distributed variables are expressed as mean ± standard deviation (SD), and non-parametric variables as median and interquartile range (IQR). Student t test and Mann–Whitney U test were used for the comparison of parametric and non-parametric variables, respectively.

Spearman correlation coefficients were calculated to assess the correlation between predialysis cTnI and intradialysis change in cTnI levels with patients' characteristics. Multivariable logistic regression analyses were performed to identify patient characteristics that are independently associated with predialysis cTnI levels and the intradialysis change in cTnI levels. The multivariable analysis included all variables with $p<0.1$ in the correlation analyses. Exposure was calculated from baseline until the date of death and/or first MACE with censoring for renal transplantation. Unadjusted and adjusted relative risks and hazard ratios for mortality and MACE were calculated using Cox-regression hazard models. Survival models were adjusted for age, sex, previous MACE, and dialysis vintage. For the analysis of the prognostic effect of postdialysis cTnI levels and the intradialysis change in cTnI levels, the models were also corrected for the predialysis cTnI level. All tests were two-sided and statistical significance was accepted at the 0.05 levels. All analyses were performed in STATA version 11 (StataCorp LP 2009, College Station, TX, USA).

Results

Patients

A total of 90 patients participated in this study. Demographic and clinical characteristics at baseline are shown in Table 1. The median age was 67 (IQR 56–75; range 23–87) years and 57% of patients were male. Patients were on dialysis for a median of 3.5 (IQR 1.5–5.5) years. Eighteen percent of patients had diabetes, and 81% had hypertension. Previous MACE was documented in 40% of patients of whom 14% had history of myocardial infarction, 19% had previous PCI or CABG, 3% had a history of unstable angina pectoris, 14% had a history of cerebrovascular events, and 5% had previous peripheral vascular disease. LVH was present in 16% of patients. Residual diuresis, defined as urine output ≥500 mL per 24 h was present in 20% of patients.

Predialysis cTnI.

The median (IQR) predialysis cTnI level was 20 ng/L (11–38). Predialysis cTnI levels ≥28 ng/L were present in 31 patients (34%). Predialysis cTnI levels were significantly correlated with age (r=0.5; p<0.001), male gender (r=0.3; p=0.02), diabetes (r=0.2; p=0.05), previous MACE (r=0.4; p<0.001), dialysis vintage (r=0.3; p=0.004), presence of hypertension (r=0.3; p=0.003) and had a trend toward a significant

Table 1 Demographic and clinical characteristics of the 90 patients at baseline.

Age, years [median (IQR)]	67 (56-75)
Males, n (%)	52 (57)
Dialysis vintage, years [median (IQR)]	3.5 (1.5-5.5)
Primary renal diagnosis, n (%)	
Hypertension	14 (16)
Diabetes	6 (7)
Glomerulonephritis	6 (7)
ADPKD	5 (6)
Obstructive uropathy	5 (6)
IgA nephropathy	2 (2)
	33 (37)
Others	19 (21)
Unknown	
Diabetes, n (%)	16 (18)
Hypertension, n (%)	73 (81)
History of MACE, n (%)	36 (40)
LVH, n (%)	14 (16)
Kt/V [median (IQR)]	4.1 (3.6-4.7)
Residual diuresis, n (%)	22 (20)
Pre-HD systolic blood pressure, mmHg (mean ± SD)	143 ± 20
Pre-HD diastolic blood pressure, mmHg (mean ± SD)	76 ± 13
BMI, kg/m^2 [median (IQR)]	24.5 (21.9-27.7)
Cardiovascular drugs, n (%)	
Aspirin	55 (61)
β-Blockers	47 (52)
Calcium antagonists	6 (7)
ACE inhibitor	4 (4)
Statin	29 (32)

Data are presented as mean ± SD in case of normal distribution and as median (interquartile range) in case of skewed distribution IQR, interquartile range; n, number; ADPKD, adult dominant polycystic kidney disease; MACE, major adverse cardiovascular events; LVH, left ventricular hypertrophy; HD, hemodialysis; BMI, body mass index; ACE, angiotensin converting enzyme.

correlation with predialysis systolic blood pressure (r=0.2; p=0.08). In multivariable analysis, only age (β: 0.01; CI: 0.003–0.012; p=0.003), gender (β: 0.14; CI: 0.01–0.26; p = 0.04), and previous MACE (β: 0.16; CI: 0.03–0.30; p=0.021) remained significantly associated with higher predialysis cTnI levels.

Intradialysis changes in cTnI

Postdialysis cTnI levels were significantly higher than predialysis levels (p<0.001) (Figure. 1). Overall, the median (IQR) absolute change in cTnI levels during hemodialysis was +3 ng/L (0–8 ng/L). cTnI levels increased during dialysis in 66% of patients, remained stable in 18% of patients, and decreased in 17% of patients. Patients with a rise in cTnI were significantly older [70 (IQR 58–77) vs 59 years (IQR 51–68); p=0.007] and had a trend toward a longer dialysis vintage [4.5 (IQR 1.5–6.5) vs 2.5 years (IQR 1.5–4.5); p=0.108]. Three patients had a pronounced rise in cTnI levels during hemodialysis (Figure. 1). None of these patients had complaints or symptoms that were suggestive of cardiac ischemia. The characteristics of these patients were comparable with the total group of patients that had a rise in cTnI levels during dialysis. Postdialysis cTnI levels ≥28 ng/L were present in 41 patients (46%).

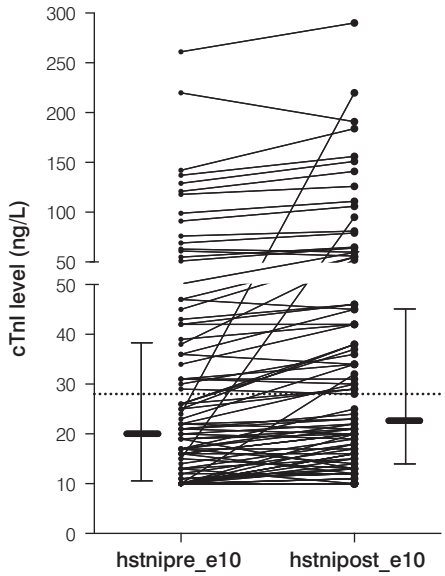

Figure 1 Individual intradialysis change of cTnI levels with median and interquartile range for the whole group (n=90).

The horizontal broken lines indicate the upper range of the reference value for the absence of myocardial damage (28 ng/L).

The intradialysis change in cTnI was significantly correlated with age (r=0.2; p=0.04), dialysis vintage (r=0.2; p=0.05), and predialysis cTnI levels (r=0.3; p=0.005). There was no correlation between the intradialytic change in cTnI levels and ultrafiltration volume during dialysis (r=-0.06; p=0.591), presence of diabetes (r=0.06; p=0.596), and presence of LVH (r=-0.07; p=0.507). In multivariable analysis, only dialysis vintage showed a trend toward an association with the intradialysis change in cTnI (β: 0.01; CI: -0.001 to 0.02; p=0.09).

Prognostic effect of pre-, post-, and intradialysis change in cTnI levels

The total follow-up time was 260 patient years. During this follow-up, 24 patients developed MACE and 40 patients died. As shown in Table 2, both predialysis and postdialysis cTnI levels were significantly associated with an increased incidence of MACE (p=0.001 and <0.001, respectively). However, after correction for age, gender, dialysis vintage, and previous MACE, only postdialysis cTnI level remained significantly associated with an increased incidence of MACE (p=0.03). Notably, the association between postdialysis cTnI and the incidence of MACE remained significant after

Table 2 Prognostic effect of pre- and postdialysis cTnI levels.

	HR/10ng/L	95% CI	*p* value
Predialysis cardiac troponin I			
MACE			
Crude	1.12	1.05-1.20	0.001
Adjusted[a]	1.05	0.97-1.14	0.192
All-cause mortality			
Crude	1.05	0.99-1.10	0.08
Adjusted[a]	1.00	0.94-1.07	0.979
Postdialysis cardiac troponin I			
MACE			
Crude	1.15	1.08-1.22	<0.001
Adjusted[a,b]	1.21	1.06-1.38	0.005
All-cause mortality			
Crude	1.03	0.98-1.08	0.210
Adjusted[a,b]	0.90	0.75-1.08	0.250

HR, hazard ratio; MACE, major adverse cardiovascular events
[a] Adjusted for age, gender, dialysis vintage, residual diuresis, and previous MACE
[b] Predialysis cardiac troponin I added to the model

correction for predialysis cTnI levels. There was no significant association between predialysis and postdialysis cTnI levels and all-cause mortality (Table 2).

As shown in Table 3, a rise in cTnI during hemodialysis was significantly associated with an increased incidence of MACE ($p<0.001$), but not with all-cause mortality ($p=0.689$). The association with the incidence of MACE remained significant after correction for age, gender, previous MACE, dialysis vintage, and predialysis cTnI levels ($p=0.003$).

Table 3 Prognostic effect of intra-HD change in cTnI levels.

	HR/10ng/L	95% CI	*p* value
Change in cTnI			
MACE			
Crude	1.25	1.11-1.41	<0.001
Adjusted[a]	1.21	1.06-1.38	0.005
All-cause mortality			
Crude	0.97	0.84-1.12	0.689
Adjusted[a]	0.90	0.75-1.08	0.250

HR, hazard ratio; MACE, major adverse cardiovascular event
[a] Adjusted for age, gender, dialysis vintage, residual diuresis, previous MACE, and predialysis cTnI level.

Discussion

This is the first study on the determinants and the prognostic significance of intradialysis changes of cTnI levels. The main findings of this study are, first, that cTnI levels increased significantly during hemodialysis and, second, that a greater intradialysis rise in cTnI was independently associated with an increased incidence of cardiovascular events but not with all-cause mortality.

Although the prognostic significance of cTnT is well described[4,16-20], there is scarce data on the prognostic significance of cTnI levels in hemodialysis patients[21]. One reason may be the low proportion of patients detected in abnormal range with conventional assays. Recently, it has been recognized that the use of sensitive cTnI assays has led to the detection of a larger proportion of dialysis patients with elevated cTnI levels[6,22]. Until now, only one study has used sensitive cTnI assays to evaluate the prognostic significance of predialysis cTnI levels[6]. In their study in 50 hemodialysis patients, Gaiki et al.[6] showed that patients with cTnI levels >0.034 ng/mL had a

significantly higher incidence of cardiovascular events but no difference in all-cause mortality. In line with this study we also found that higher predialysis cTnI levels were associated with a higher incidence of MACE, but not with all-cause mortality. However, after correction for other cardiovascular risk factors (age, gender, dialysis vintage, and previous MACE) the association between elevated predialysis cTnI levels and cardiovascular outcome lost its significance, an analysis that was lacking in the former study. Interestingly, we found that postdialysis cTnI levels were independently associated with the incidence of MACE but, again, not with all-cause mortality. Notably, the prognostic effect of postdialysis cTnI levels remained significant after correction for predialysis cTnI levels. This suggests that postdialysis cTnI levels may have additional prognostic value as compared with predialysis cTnI levels.

Previous studies on the effect of the hemodialysis procedure on cTnI levels have yielded conflicting results. Some studies reported no overall change[9-11] whereas other studies found a decrease[3,12] in cTnI levels during hemodialysis. These studies were all performed using conventional cTnI assays. Using a sensitive assay we found that cTnI levels rose during hemodialysis in the majority (66%) of patients. Although it is assumed that cTnI is not cleared by diffusive hemodialysis using low-flux dialysers because of its relatively high molecular weight (23,876 Da), we cannot exclude that some cTnI was removed from the circulation by clearance or absorption to the dialysis membrane[3]. This may have resulted in underestimation of the actual intradialysis rise in cTnI levels. We found that a greater rise of cTnI was significantly associated with higher age, longer dialysis vintage, and higher predialysis cTnI levels. However, in the multivariable analysis these associations were not significant anymore, although dialysis vintage showed a trend toward a significant association with the intradialysis change in cTnI. This trend may suggest increased susceptibility for subclinical myocardial injury during hemodialysis with increasing dialysis duration, e.g. due to progression of the uremia-associated myocardial damage[23].

This study shows for the first time that a rise in cTnI levels during hemodialysis is associated with an increased incidence of MACE. Notably, the observed rise in cTnI during hemodialysis was relatively small compared with the dynamic rise in cTnI that is diagnostic in myocardial ischemia in clinical practice. However, since cTnI is a highly specific marker of myocardial damage, this finding suggests that conventional hemodialysis may elicit subtle cardiac injury. This observation adds to the increasing evidence that the hemodialysis procedure itself has acute negative effects on cardiac perfusion and function[24]. By applying PET scanning in hemodialysis patients, we and others have demonstrated that hemodialysis sessions elicit acute reductions in myocardial perfusion, even in the absence of ultrafiltration[7,8,25]. In some patients the fall in myocardial blood flow was severe enough to result in reversible left ventricular systolic dysfunction (hypokinesia/akinesia), especially in regions with the greatest fall in myocardial perfusion indicative of ischemia[7,8]. Two recent studies[26,27] showed with

echocardiography that the prevalence of such hemodialysis-induced regional systolic left ventricular dysfunction is high. Future studies should address the question whether rises in cTnI levels during hemodialysis may help to identify patients with hemodialysis-induced regional systolic left ventricular dysfunction.

This study has important implications for clinical practice. First, we confirm the results of two recent studies that a considerable proportion of hemodialysis patients without clinical cardiac symptoms has elevated pre- and postdialysis cTnI levels in the myocardial damage range when measured with a sensitive assay[6,22], although cTnI levels are less frequently elevated compared with cTnT levels[4,5]. Second, it has been suggested that familiarity with a dialysis patient's baseline, i.e. predialysis, troponin level might aid in the diagnosis of an acute coronary syndrome if the patient has a level that is higher than this baseline value in the appropriate clinical setting[22]. Although a rise in cardiac troponins within hours generally argues in favor of an acute cardiac cause[28], this study shows that cTnI levels measured with a sensitive assay rise during hemodialysis in a significant proportion of asymptomatic patients. This clearly limits the diagnostic use of a dynamic rise in cTnI from the predialysis to the postdialysis period. Third, at the same time this study shows that an intradialysis rise of cTnI, although relatively small, should not be discarded as meaningless since it is associated with an increased incidence of cardiovascular events.

We acknowledge that our study has limitations. The study population is relatively small. However, the long follow-up period and, consequently, the relatively high number of events during follow-up increased the statistical power of this study with regard to the analysis of the association between intradialysis rises in cardiac troponins and outcome. Our findings should be confirmed in other patient cohorts before definite conclusions can be drawn. Plasma levels of cTnI were not corrected for hemo-concentration. However, we did not find an association between intradialysis change in cTnI and ultrafiltration volume. Finally, in this study we focussed on the association between patient-related factors and intradialytic changes in cTnI levels. Future studies should address whether hemodialysis-related factors such as a change in acid–base balance and electrolytes or an inflammatory response due to blood–membrane contact are associated with rises in cTnI.

In conclusion, not only pre- but also postdialysis cTnI levels are elevated in a large proportion of patients. A greater intradialysis rise in cTnI is independently associated with an increased incidence of cardiovascular events, suggesting that the hemodialysis procedure itself may have deleterious effects on the heart.

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Chapter 4

Hemodialysis-Induced Regional Left Ventricular Systolic Dysfunction: Prevalence, Patient and Dialysis Treatment-Related Factors, and Prognostic Significance

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Summary

Background and objectives: The hemodialysis procedure may acutely induce regional left ventricular systolic dysfunction. This study evaluated the prevalence, time course, and associated patient- and dialysis-related factors of this entity and its association with outcome.

Design, setting, participants, & measurements: Hemodialysis patients (105) on a three times per week dialysis schedule were studied between March of 2009 and March of 2010. Echocardiography was performed before dialysis, at 60 and 180 minutes intradialysis, and at 30 minutes postdialysis. Hemodialysis-induced regional left ventricular systolic dysfunction was defined as an increase in wall motion score in more than or equal to two segments.

Results: Hemodialysis-induced regional left ventricular systolic dysfunction occurr ed in 29 (27%) patients; 17 patients developed regional left ventricular systolic dysfunction 60 minutes after onset of dialysis. Patients with hemodialysis-induced left ventricular systolic dysfunction were more often male, had higher left ventricular mass index, and had worse predialysis left ventricular systolic function (left ventricular ejection fraction). The course of blood volume, BP, heart rate, electrolytes, and acid–base parameters during dialysis did not differ significantly between the two groups. Patients with hemodialysis-induced regional left ventricular systolic dysfunction had a significantly higher mortality after correction for age, sex, dialysis vintage, diabetes, cardiovascular history, ultrafiltration volume, left ventricular mass index, and predialysis wall motion score index.

Conclusions: Hemodialysis induces regional wall motion abnormalities in a significant proportion of patients, and these changes are independently associated with increased mortality. Hemodialysis-induced regional left ventricular systolic dysfunction occurs early during hemodialysis and is not related to changes in blood volume, electrolytes, and acid–base parameters.

Introduction

Cardiac mortality and morbidity is much higher in hemodialysis patients compared with the general population[1,2]. The excess mortality cannot be explained by traditional risk factors[3]. It is increasingly recognized that the hemodialysis procedure itself may be a risk factor in developing cardiac dysfunction[4-7]. By applying positron emission tomography scanning during hemodialysis, we and others showed that hemodialysis sessions reduce myocardial blood flow[8,9]. In some patients, the fall in myocardial blood flow was severe enough to result in reversible left ventricular (LV) systolic dysfunction, especially in regions with the greatest fall in myocardial blood flow[8,9]. Reversible regional LV systolic dysfunction during hemodialysis has also been shown in several relatively small studies using serial echocardiography[5,10]. In a larger study population, the work by Burton et al.[11] recently showed that hemodialysis-induced LV systolic dysfunction occurred in more than one-half of their patients and was associated with higher all-cause mortality. However, the echocardiographic technique to assess the development of hemodialysis-induced LV systolic dysfunction in these studies[5,10,11] is not routinely used in clinical patient care. Moreover, the time course of this entity in relation to blood volume and hemodynamic changes is not well delineated. Also, the relationship between hemodialysis-induced LV systolic dysfunction and relevant patient characteristics, like predialysis LV function and LV mass, has not been studied in detail. Finally, the association between hemodialysis-induced LV systolic dysfunction and specific dialysis-related factors, such as electrolyte and acid–base shifts, is presently unknown but relevant, because these factors can influence cardiac function and are modifiable[12-15]. In this study, we assessed the acute effects of hemodialysis on global and regional LV systolic function by serial echocardiography before, during, and after dialysis using the routine systolic measurements for clinical practice that are recommended by the American Society of Echocardiography[16]. In addition, we studied the association between hemodialysis-induced LV systolic dysfunction and patient and dialysis-related factors and its impact on outcome.

Materials and Methods

Patients and Study Design

Hemodialysis patients from the Dialysis Center Groningen and the University Medical Center Groningen were eligible for this study if they were treated with hemodialysis for more than 3 months and were on a three time per week hemodialysis schedule. Patients with severe heart failure (New York Heart Association functional classification, stage IV) and patients who did not have an adequate window for echocardiography imaging were excluded.

Patients were studied at the dialysis session after the longest interdialytic interval (3 days). The dialysis duration was 4 hours. Patients' characteristics were assessed at entry into the study. Diabetes was defined as fasting blood glucose>6 mmol/L or the use of antidiabetic drugs. Hypertension was defined as a predialysis systolic BP>140 mmHg and/or diastolic BP>90 mmHg or the use of antihypertensive drugs. Cardiovascular history was defined as any history of ischemic heart disease, congestive heart failure, coronary artery bypass grafting, percutaneous coronary intervention, stroke, or peripheral vascular disease.

BP and heart rate were measured 30 minutes before the start of hemodialysis, every 30 minutes during hemodialysis, and 30 minutes postdialysis. Blood samples were collected at the start of hemodialysis, 60 and 180 minutes intrahemodialysis, and the end of the dialysis session. Blood was sampled for the immediate determination of hematocrit, plasma albumin, acid-base parameters, sodium, potassium, magnesium, and total and ionized serum calcium levels. The change in blood volume was calculated from the change in hematocrit ($[(Ht_0/Ht_1)-1]x100$). Ht_0 and Ht_1 represent the hematocrit at the start of hemodialysis and during hemodialysis, respectively. Ultrafiltration rate was expressed in milliliters per hour per kilogram by dividing the ultrafiltration volume by dialysis session length and target weight as previously described[17]. Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentration according to the second-generation logarithmic Daurgirdas equation[18]. The nutritional status of the patients was assessed with the seven-point subjective global assessment. This seven-point subjective global assessment has been described and validated in dialysis patients in The Netherlands Cooperative Study on the Adequacy of Dialysis[19]. A score of seven indicates a normal nutritional status, and a score of one indicates severe protein energy wasting. The study was performed according to the Declaration of Helsinki and approved by the Medical Ethical Committee of the University Medical Center Groningen. All patients gave written informed consent. The study was performed between March of 2009 and March of 2010.

Dialysis Settings

All patients were on bicarbonate dialysis with a low-flux polysulfone hollow-fiber dialyser (F8; Fresenius Medical Care, Bad Hamburg, Germany). Blood flow and dialysate flow rates were 250–350 ml/min and 500 ml/min, respectively. Dialysate temperature was 36.0°C in all patients. Dialysate composition was sodium (139 mmol/L), potassium (1.0 or 2.0 mmol/L), calcium (1.5 mmol/L), magnesium (0.5 mmol/L), chloride (108 mmol/L), bicarbonate (34 mmol/L), acetate (3.0 mmol/L), and glucose (1.0 g/L). We used constant ultrafiltration rate and dialysate conductivity. The water for hemodialysis complied with the requirements of the European Pharmacopoeia (<100 colony forming units/ml and <0.25 endotoxin units/ml). Patients received

a light meal after the echocardiography at 60 minutes intradialysis. All patients were dialyzed in supine position, which was convenient for echocardiography and excluded the effect of posture changes on blood volume.

Echocardiography Examination

A dedicated team of three experienced technicians performed two-dimensional echocardiography using a General Electric VIVID 7 system with a 2.5-mHz probe. Echocardiography was performed four times: before hemodialysis, at 60 and 180 minutes after the start of hemodialysis, and at 30 minutes after the end of hemodialysis. One experienced technician (Y.M.H.) performed all the analyses offline according to the guidelines of the European Society of Echocardiography[20]. At least three consecutive heartbeats in each view were acquired. Global and regional systolic function was evaluated by left ventricular ejection fraction (LVEF) and wall motion score index (WMSI), respectively. LVEF was calculated using the biplane Simpson's method. WMSI was evaluated according to the 16-segments model (as recommended by the American Society of Echocardiography)[16] by a single technician (Y.M.H) who was blinded to the order of echocardiography studies. For each patient, the number of LV regions (from a total of 16) that developed new (not present before hemodialysis) regional wall motion abnormalities (RWMAs) during hemodialysis was calculated. RWMA was defined as an increase in WMS in the specific LV segment occurring at 60 minutes intradialysis, 180 minutes intradialysis, or 30 minutes posthemodialysis compared with predialysis. Hemodialysis-induced LV systolic dysfunction was defined as the development of new RWMAs in two or more LV segments compared with predialysis. LV mass index was calculated as described previously[21]. Left ventricular hypertrophy (LVH) was defined as LV mass index>95 g/m2 for women and >115 g/m2 for men.

Statistical Analyses

Data are reported as mean ± SD for continuous variables with normal distributions, median (interquartile range [IQR]) for skewed variables, and number (percent) for categorical data. Comparisons with baseline were made by paired t, Wilcoxon signed rank, and chi-squared tests for parametric, nonparametric, and categorical variables, respectively. The survival curves for the patients with and without hemodialysis-induced LV systolic dysfunction were computed by the Kaplan–Meier method, and differences between the curves were compared by log-rank test. The multivariate Cox proportional hazards model was used to evaluate the association between hemodialysis-induced LV systolic dysfunction and all-cause mortality (adjusted for age, sex, dialysis vintage, diabetes, cardiovascular history, ultrafiltration volume, LV mass index, and predialysis WMSI). Two-sided P value 0.05 was considered significant. All statistical analyses were performed with STATA version 11 (StataCorp LP, College Station, TX).

Results

Patient Characteristics

The recruitment process of participants is outlined in Figure 1; 109 patients participated in this study, and 4 patients were excluded from the analysis, because it was not possible to reliably assess the per-segment LV function during hemodialysis. The patient characteristics of the remaining 105 patients are shown in Table 1. The median (IQR) age was 66 (51–75) years, and 64.8% were male (Table 1). They had been treated with hemodialysis for a median of 21.4 (IQR=7.8–48.5) months; 22% of patients had diabetes, and 80% of patients had hypertension. The average total ultrafiltration volume and ultrafiltration rate during hemodialysis were 2.6 ± 0.8 L and 8.5 ± 2.6 ml/kg per hour, respectively (Table 1).

Echocardiographic Parameters

Thirty-seven (35.2%) and forty-two (40.0%) patients had prehemodialysis LVEF<50% and WMSI>1, respectively. LVH was present in 25 (23.8%) patients.

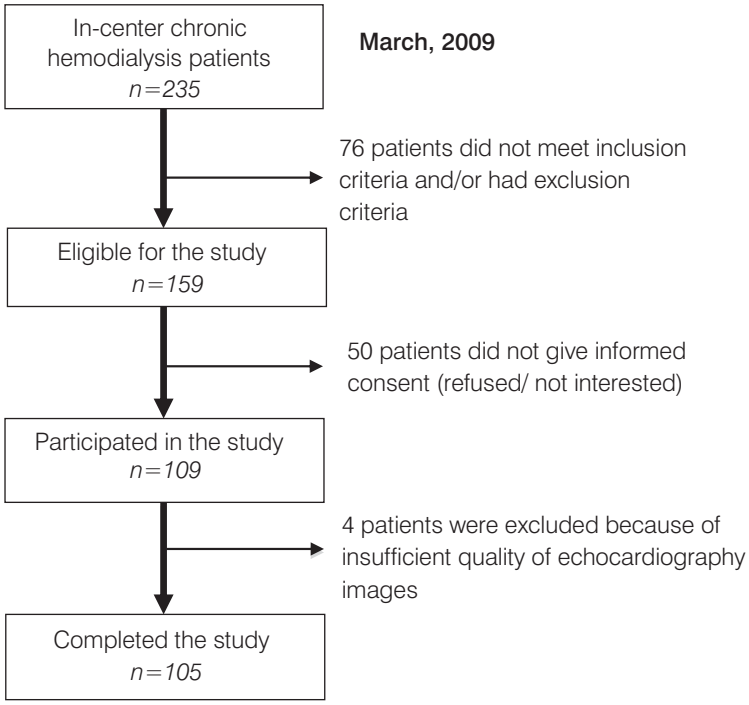


Figure 1 Recruitment process of study participants.

None of the participating patients had angina or any other symptom of myocardial ischemia during or after the hemodialysis session; 29 patients (27%) developed new RWMA in two or more LV segments at 60 minutes intradialysis, 180 minutes intradialysis, or 30 minutes postdialysis, and thus, they had hemodialysis-induced LV systolic dysfunction. Of these patients, 17 (59%) patients had RWMA in more than or equal to two segments at 60 minutes intradialysis, when their blood volume was only -0.9±4.5% lower compared with the start of hemodialysis.

As shown in Table 1, patients with hemodialysis-induced LV systolic dysfunction were more often male ($p=0.05$), had a higher LV mass index ($p=0.05$), had a higher predialysis WMSI ($p<0.001$), and had a lower predialysis LVEF ($p=0.008$). The proportion of patients with LVH did not differ significantly between patients with (21%) and without (25%) hemodialysis-induced LV systolic dysfunction ($p=0.64$).

Hemodynamic Parameters

Figure 2 shows the course of systolic and diastolic BPs. Predialysis systolic BP was lower (132.9 ± 21.7 versus 143.4 ± 25.0, $p=0.06$) and predialysis heart rate was slightly higher (74 [IQR=66–86] versus 71 [IQR=63–82], $p=0.30$) in patients with compared with patients without hemodialysis induced LV systolic dysfunction. The difference in predialysis heart rate and systolic BP between the two groups persisted until the end of the hemodialysis session. At the end of hemodialysis, heart rate tended to be higher in patients with compared with patients without hemodialysis-induced LV systolic dysfunction (84 [IQR=77–93] versus 77 [IQR=66–86], ($p=0.06$).

The total ultrafiltration volume and ultrafiltration rate during hemodialysis did not differ significantly between patients with and without hemodialysis-induced LV systolic dysfunction (Table 1). Blood volume decreased during hemodialysis as a result of ultrafiltration. At 60 minutes of hemodialysis, the change in blood volume was -0.9 ± 4.5% and -1.2 ± 3.4% in patients with and without hemodialysis induced LV systolic dysfunction, respectively ($p=0.41$). At the end of the hemodialysis session, blood volume was significantly ($p<0.001$) lower compared with the start of hemodialysis in both groups (-4.3 ± 6.1% and -4.5 ± 4.6% in patients with and without hemodialysis-induced LV systolic dysfunction, respectively). As shown in Figure 2, the blood volume course did not differ between patients with and without hemodialysis-induced LV systolic dysfunction.

Acid–Base and Electrolyte Changes

Plasma bicarbonate levels and blood pH rose significantly ($p<0.001$) during hemodialysis in both groups (Figure 3), but the course of bicarbonate levels and blood pH did not differ significantly between patients with and without hemodialysis-induced LV systolic dysfunction. As shown in Figure 3, plasma levels of sodium, potassium, ionized calcium, albumin-corrected calcium, and magnesium did not

Table 1 Patient characteristics.

	All patients (n=105)	No hemodialysis-induced regional LV dysfunction (n=76)	hemodialysis-induced regional LV dysfunction (n=29)	*p* value
Median age in years (IQR)	66 (51-75)	64 (50-75)	69 (58-78)	0.18
Male sex (n)	68 (64.8)	45 (59.2)	23 (79.3)	0.05
Median dialysis vintage in months (IQR)	21.4 (7.8-48.5)	24 (8.3-48.3)	18.4 (5.5-49.7)	0.69
Diabetes (n)	23 (21.9)	19 (25.0%)	4 (13.8%)	0.28
Hypertension (n)	84 (80.0)	61 (80.3)	23 (79.3)	0.95
Cardiovascular history(n)	23 (21.9)	15 (19.7%)	8 (27.6%)	0.39
BMI (kg/m^2; IQR)	25.2 (23.0-28.1)	25.2 (22.6-28.3)	25.2 (23.2-27.8)	0.88
Primary renal disease (n)				
Hypertension	17 (16.2)	12 (15.8%)	5 (17.2%)	0.86
Diabetes	13 (12.4)	11 (14.5%)	2 (6.9%)	0.29
ADPKD	14 (13.3)	10 (13.6%)	4 (13.8%)	0.93
FSGS	10 (9.5)	8 (10.5%)	2 (6.9%)	0.57
IgA nephropathy	4 (3.8)	4 (5.3%)	0	0.21
Chronic pyelonephritis	1 (1.0)	1 (1.3%)	0	0.54
Glomerulonephritis	13 (12.4)	10 (13.2%)	3 (10.3%)	0.70
Other diagnoses	16 (15.2)	10 (13.2%)	6 (20.6%)	0.21
Unknown	17 (16.2)	10 (13.2%)	7 (24.1%)	0.17
Medication (n)				
Aspirin	57 (54.3)	46 (60.5)	11 (37.9)	0.04
CCB	14 (13.3)	12 (15.8)	2 (6.9)	0.23
β-Blocker	60 (57.1)	45 (59.2)	15 (51.7)	0.49
ACE inhibitor	10 (9.5)	8 (10.5)	2 (6.9)	0.57
ARB	14 (13.3)	10 (13.2)	4 (13.8)	0.34
Statin	20 (19.1)	14 (18.4)	6 (20.7)	0.79

Median SGA (IQR)	6 (6-7)	6 (6-7)	6 (5-7)	0.77
Hematocrit (mean±SD)	35.0±3.7	35.1±4.0	34.6±3.0	0.53
Median Albumin (g/l; IQR)	39 (37-41)	39 (37-42)	39 (37-41)	0.64
Median Phosphate (mmol/l; IQR)	1.7 (1.3-1.9)	1.7 (1.3-2.0)	1.6 (1.4-1.9)	0.92
Median Kt/V (IQR)	4.3 (3.8-4.7)	4.3 (3.8-4.7)	4.0 (3.9-4.5)	0.36
Ultrafiltration volume (L; mean±SD)	2.6±0.8	2.5±0.7	2.60±0.9	0.83
Ultrafiltration rate (ml/kg/per hour; mean±SD)	8.5±2.6	8.6±2.5	8.3±3.0	0.59
LV mass index (g/m^2; mean±SD)	93.3±26.0	89.9±24.6	101.7±27.9	0.05
LVH (n)	25 (23.8)	19 (25)	6 (20.7)	0.64
Median predialysis WMSI (IQR)	1.00 (1.00-1.13)	1.00 (1.00-1.03)	1.21 (1.06-1.44)	<0.001
Predialysis LVEF (mean±SD)	50.0±10.4	51.8±9.5	45.3±10.4	0.008

Abbreviations: LV, left ventricular; IQR, interquartile range; BMI, body mass index; ADPKD, adult dominant polycystic kidney disease; FSGS, focalsegmental glomerulosclerosis; CCB, calcium channel blocker; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SGA, subjective global assessment; LVH, LV hypertrophy; WMSI, wall motion score index; LVEF, LV ejection fraction.

differ significantly between patients with and without hemodialysisinduced LV systolic dysfunction.

Prognostic Significance of Hemodialysis-Induced Regional LV Dysfunction

The median (range) duration of follow-up in surviving patients was 16.4 (12.3–24.5) months. The total follow-up time was 130.8 patient years. During follow-up, 9 (31%) patients that developed hemodialysis-induced LV systolic dysfunction and 6 (8%) patients that did not develop hemodialysis-induced LV dysfunction died (p=0.002) (Figure 4); 60% of deaths had a cardiac cause. The difference in mortality between the two groups remained statistically significant after correction for age, sex, dialysis vintage, diabetes, cardiovascular history, ultrafiltration volume, LV mass index, and predialysis WMSI (hazard ratio=4.6, confidence interval=1.15–18.5, p=0.03). As shown in Figure 5, survival worsened with an increased number of abnormal LV

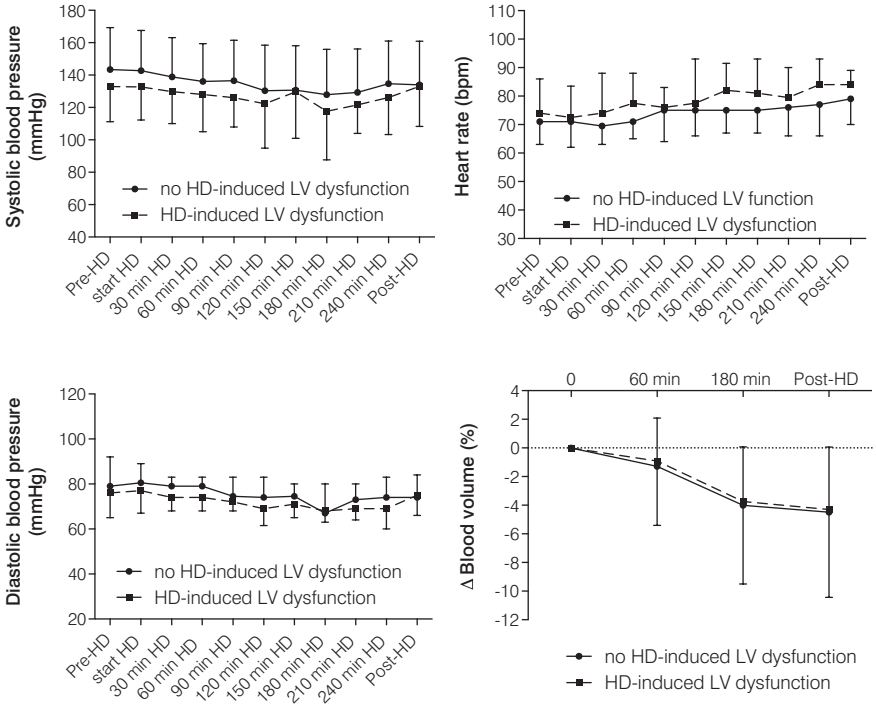


Figure 2 The course of systolic and diastolic BP, heart rate, and blood volume change in patients with and without hemodialysis-induced regional left ventricular (LV) systolic dysfunction (mean ± SD).

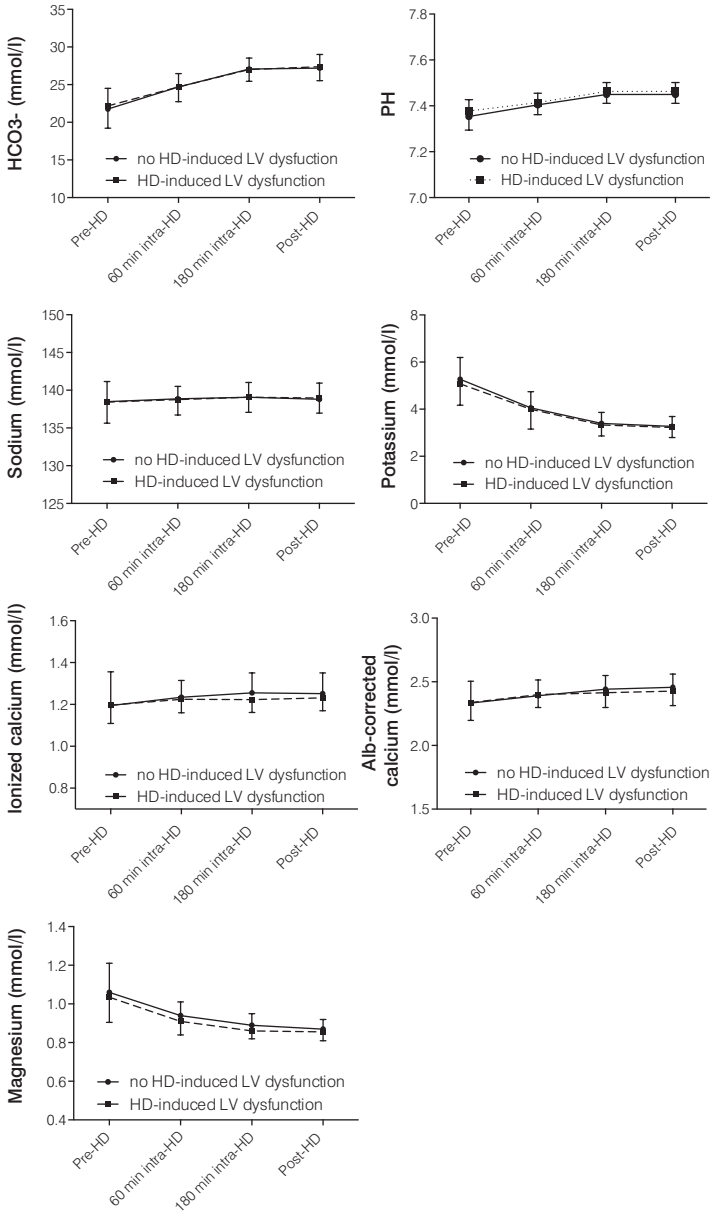
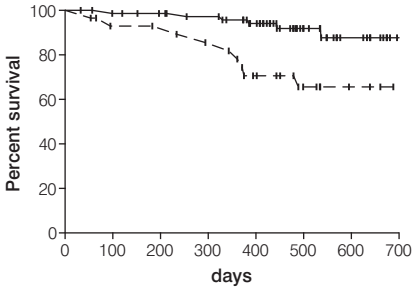


Figure 3 The course of acid–base parameters (plasma bicarbonate and blood pH) and electrolytes (plasma sodium, potassium, ionized and albumin-corrected calcium, and magnesium levels) in patients with and without hemodialysis-induced regional LV systolic dysfunction (mean ± SD).

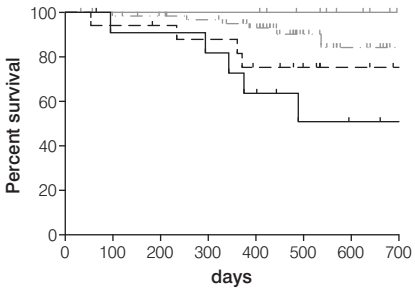
segments developing during hemodialysis (overall difference between groups by log-rank test was p=0.009).



Numbers at risks					
No HD-induced LV systolic dysfunction	29	25	18	7	3
HD-induced LV systolic dysfunction	76	70	58	13	1

no HD-induced LV systolic dysfunction
HD-induced LV systolic dysfunction

Figure 4 Kaplan–Meier curve of all-cause mortality in patients with and without hemodialysis-induced regional LV systolic dysfunction.



Numbers at risk					
0 abnormal segment	65	59	47	8	1
1 abnormal segment	11	11	11	5	0
2-3 abnormal segments	17	15	11	4	1
≥4 abnormal segments	12	10	7	3	2

0 abnormal segment
1 abnormal segment
2-3 abnormal segments
≥4 abnormal segments

Figure 5 Kaplan–Meier curve of all-cause mortality in patients who did not develop regional wall abnormalities and patients with an increasing number of LV segments developing regional wall motion abnormalities during hemodialysis.

Discussion

In this study, we found that LV regional systolic dysfunction developed during hemodialysis in about one-quarter of patients. In the majority of these patients, it occurred early during hemodialysis. Hemodialysis-induced regional LV systolic dysfunction was associated with male sex, higher LV mass index, and pre-existent LV dysfunction, but it was not associated with dialysis treatment-related factors, like changes in blood volume, electrolytes, or acid–base parameters. Hemodialysis-induced regional LV systolic dysfunction was independently associated with higher all-cause mortality.

The present study confirms earlier observations that hemodialysis may acutely induce regional LV dysfunction in a substantial proportion of patients[8,9,11,22]. However, we found a lower prevalence of hemodialysis-induced regional LV dysfunction than previously reported[11]. This finding may be explained by differences in the study population, like a lower proportion of patients with diabetes, cardiovascular history, and LVH in our study. A second explanation might be the difference in the method used for the evaluation of regional LV systolic dysfunction. We used standard echocardiographic evaluation of regional LV function according to the guidelines of the American Society of Echocardiography[16], which is validated for routine clinical application, whereas the work by Burton et al.[11] used the measurement of regional fractional shortening to evaluate regional LV systolic function. Although this method is quantitative and reproducible, it is not recommended in current practice guidelines.

A remarkable finding in our study was the observation that, in many patients, regional LV systolic dysfunction developed early during hemodialysis (i.e., within 1 hour of the start of the dialysis session). At that time, the decrease in blood volume was only marginal. Notably, the ultrafiltration volume and the ultrafiltration rate as well as the change in blood volume did not differ between patients with and without hemodialysis-induced regional LV systolic dysfunction. These observations suggest that intradialytic blood volume changes do not have a dominant role in the development of hemodialysis-induced regional LV dysfunction. In a previous study, using cardiac positron emission tomography scanning during hemodialysis, we also observed that the reduction in myocardial blood flow occurred early (within 30 minutes of the start of dialysis) during hemodialysis, even in the absence of ultrafiltration[8]. In that study, there was no correlation between total ultrafiltration volume and the change in myocardial blood flow during hemodialysis. However, another study found that ultrafiltration volume was an independent predictor of the development of regional LV systolic dysfunction during hemodialysis[11].

In the present study, patients who developed hemodialysis-induced LV systolic dysfunction had more often an impaired LV systolic function before hemodialysis. This finding suggests that patients with impaired predialysis systolic function are more susceptible to the cardiac stress induced by the hemodialysis procedure.

Alternatively, the impaired predialysis LV systolic function may be caused by repetitive hemodialysis-induced myocardial hypoperfusion (myocardial stunning), which may eventually result in fixed LV dysfunction[11]. Interestingly, we found that patients who developed hemodialysis-induced LV systolic dysfunction had a higher LV mass index compared with patients with preserved LV systolic function during hemodialysis. It has previously been shown that a higher LV mass index in dialysis patients is associated with a relative reduction in capillary density (myocyte–capillary mismatch)[23], which may contribute to the development of ischemia.

Changes in electrolytes and acid–base parameters during hemodialysis are known to have cardiovascular effects[12-14,24,25] and might play a pathophysiological role in the development of hemodialysis-induced LV systolic dysfunction. In this study, we observed changes in electrolytes and acid–base parameters similar to those changes described previously[24,26]. However, we found no significant differences between patients with and without hemodialysis-induced LV systolic dysfunction. Therefore, it is unlikely that electrolyte and acid–base changes during hemodialysis are involved in the pathogenesis of hemodialysis-induced regional LV systolic dysfunction.

Patients with hemodialysis-induced LV systolic dysfunction had a significantly higher mortality during a median follow-up of 16.4 months. In a previous study[11], it was similarly shown that hemodialysis-induced cardiac dysfunction was associated with poor survival after 1 year. In the present study, hemodialysis-induced regional LV dysfunction seemed to be an independent risk factor for all-cause mortality, because the association remained significant after correction for other important prognostic factors, such as age, sex, dialysis vintage, diabetes, cardiovascular history, ultrafiltration volume, LV mass index, and predialysis LV systolic function.

An important limitation of this study is the lack of angiographic evaluation of coronary arteries and therefore, the inability to correlate the echocardiographic findings with underlying coronary artery disease. This limitation should be considered in future studies on the effect of hemodialysis on LV function. A second limitation is the lack of a validated echocardiographic definition of hemodialysis induced regional LV systolic dysfunction. In this study, hemodialysis-induced LV systolic dysfunction was defined as an increase in WMS in two or more LV segments compared with predialysis. The use of other cutoff values would have influenced the prevalence of this entity as well as its association with outcome, because survival decreased with an increasing number of segments developing abnormal function during hemodialysis. Our study has several strengths. First, this study is the largest study that evaluated the acute effect of hemodialysis on LV global and regional systolic function. Second, we used routine and clinically applicable echocardiographic methods to evaluate global and regional LV systolic function. Third, the echocardiographic analysis of regional LV systolic function was performed by a single technician who was blinded to the order of echocardiography studies.

In conclusion, hemodialysis induces RWMAs in a significant proportion of patients, and these changes are independently associated with increased mortality. Hemodialysis-induced regional LV systolic dysfunction occurs early during hemodialysis, and it is not related to changes in blood volume, electrolytes, and acid–base parameters.

Funding

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Chapter 5

Changes in Left Ventricular Diastolic Function During Hemodialysis Sessions

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Abstract

Background: Left ventricular diastolic dysfunction is common in hemodialysis patients and is associated with worse outcome. Previous studies have shown that diastolic function worsens from pre– to post–dialysis session, but this has not been studied during hemodialysis. We studied the evolution of diastolic function parameters early and late during hemodialysis.

Study Design: Observational study.

Setting & Participants: 109 hemodialysis patients on a thrice-weekly dialysis schedule with a mean age of 62.5 ± 15.6 (SD) years were studied between March 2009 and March 2010.

Predictor: Hemodialysis with constant ultrafiltration rate and dialysate conductivity.

Outcomes: Changes in diastolic function parameters.

Measurements: Mitral early inflow (E) and tissue Doppler early diastolic velocity (mean e') were evaluated by echocardiography predialysis, at 60 and 180 minutes intradialysis, and postdialysis. Relative blood volume changes were calculated from changes in hematocrit.

Results: Predialysis E and mean e' were 0.93 ± 0.24 m/s and 6.6 ± 2.1 cm/s, respectively. E and mean e' values decreased significantly during hemodialysis ($p<0.001$). The steepest change occurred at 60 minutes intradialysis (E,-21.4% ± 17.6% and-30.5% ± 19.2% at 60 and 180 minutes, respectively; mean e',-16.0% ± 18.6% and -19.5% ± 21.8% at 60 and 180 minutes, respectively). At 60 minutes intradialysis, changes in relative blood volume and brain natriuretic peptide level were associated significantly with the change in E but not with the change in mean e'.

Limitations: Changes in relative blood volume may not fully reflect central blood volume changes and do not capture the effect of blood loss to the extracorporal circuit. Left atrial volume was not measured.

Conclusions: Left ventricular diastolic function worsens early during a hemodialysis session. The decrease in mean e' at 60 minutes intradialysis was unrelated to changes in relative blood volume. Although this finding does not exclude a role of hypovolemia because of the limitations of the measurement of relative blood volume, it raises the possibility that non–volume-related mechanisms are involved in the early decrease in mean e' during hemodialysis.

Introduction

Cardiac mortality and morbidity rates are strongly elevated in hemodialysis patients compared with the general population[1,2]. Left ventricular (LV) hypertrophy (LVH), cardiac arrhythmias, and systolic and diastolic LV dysfunction frequently are present and contribute to the high cardiovascular event rate[3]. A variety of traditional and nontraditional risk factors have been identified, but these factors can only partly explain the high incidence of cardiac dysfunction and cardiac events[2]. It is increasingly recognized that the hemodialysis procedure itself may contribute to the high rate of cardiac mortality and morbidity[4,5]. Various studies have shown that the hemodialysis procedure is associated with electrocardiographic signs of ischemia,[6] increases in cardiac troponin levels,[7,8] acute decreases in myocardial perfusion,[9,10] development of regional LV systolic dysfunction,[4,11] and sudden cardiac death[12].

Diastolic LV dysfunction is a frequent finding in hemodialysis patients. The reported prevalence varies from 25%-87%, depending on the definition used and the patient population studied[13,14]. It generally is accepted that subclinical diastolic dysfunction is associated with increased risk of the development of overt heart failure[15]. As in the population without decreased kidney function, in dialysis patients, diastolic dysfunction is associated with reduced survival[15]. Besides uremic myocardial disease,[16,17] atherosclerotic changes in the cardiac vascular bed, and associated cardiac remodeling,[18] hemodialysis itself may predispose for progression of diastolic dysfunction. Previous studies showed a worsening of diastolic function parameters after versus before a hemodialysis session[19-23]. However, no study has evaluated diastolic function parameters during hemodialysis. The primary objective of this study therefore was to assess the acute effects of hemodialysis on diastolic function using serial echocardiographic assessments.

Methods

Patients and Study Design

Adult hemodialysis patients (aged ≥18 years) from the Dialysis Center Groningen and the University Medical Center Groningen were eligible for this study if they had been treated with hemodialysis for more than 3 months and were on a thrice-weekly dialysis schedule. Patients with severe heart failure (New York Heart Association stage IV) and patients who did not have an adequate window for echocardiographic imaging were excluded.

Patients were studied at the dialysis session after the longest interdialytic interval. We have chosen the longest interdialytic interval because during the hemodialysis session after the longest interdialytic interval, fluid changes are most prominent and

most cardiac events occur at the first dialysis day of the week. Dialysis session duration was 4 hours. Blood pressure and heart rate were measured at the start of a session, every 30 minutes during dialysis, and 30 minutes postdialysis. Blood was sampled from the arterial dialysis tubing at the start of hemodialysis, at 60 and 180 minutes intradialysis, and at the end of the dialysis session for determination of hematocrit, albumin, total and ionized calcium, magnesium, and brain natriuretic peptide (BNP) levels. Change in blood volume was calculated from the change in hematocrit: $[(Ht_0/Ht_1)-1]$ x100. Ht_0 and Ht_1 represent hematocrit at the start of hemodialysis and during dialysis, respectively. Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentrations according to the second-generation logarithmic Daugirdas equation[24].

Echocardiography was performed 4 times: before hemodialysis, at 60 and 180 minutes intradialysis, and 30 minutes postdialysis. The study was performed according to the Declaration of Helsinki and was approved by the medical ethics committee of the University Medical Center Groningen. All patients signed written informed consent. The study was performed between March 2009 and March 2010. Measurements also were performed between March 2009 and March 2010.

Patients' characteristics were assessed at entry into the study. Diabetes was defined as fasting blood glucose level >6 mmol/L or use of antidiabetic drugs. Hypertension was defined as predialysis systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg or use of antihypertensive drugs. Cardiovascular history was defined as any history of ischemic heart disease, congestive heart failure, coronary artery bypass graft, percutaneous coronary intervention, stroke, or peripheral vascular disease.

Laboratory Procedures

Blood samples were processed within 1 hour. Hematocrit was measured on a Sysmex XE-2100i Hematology analyzer (Sysmex Corp). Plasma albumin and magnesium were measured on a Roche Modular P (Roche Diagnostics). Ionized calcium was measured by an ABL-825 (Radiometer). BNP was measured by the microparticle enzyme immunoassay (Abbott Diagnostics).

Dialysis Setting

All patients were treated using bicarbonate dialysis with a low-flux polysulfone hollow-fiber dialyzer (F8; Fresenius Medical Care). Blood flow and dialysate flow rates were 250-350 and 500 mL/min, respectively. Dialysate temperature was 36.0°C in all patients. Dialysate composition was as follows: sodium, 139 mmol/L; potassium, 1.0 or 2.0 mmol/L; calcium, 1.5 mmol/L; magnesium, 0.5 mmol/L; chloride, 108 mmol/L; bicarbonate, 34 mmol/L; acetate, 3.0 mmol/L; and glucose, 1.0 g/L. We used constant ultrafiltration rate and dialysate conductivity. Ultrafiltration rate was expressed in

milliliters per hour per kilogram by dividing ultrafiltration volume by dialysis session length and target weight. The water for hemodialysis complied with the requirements of the European Pharmacopoeia (<100 colony-forming units/mL and <0.25 endotoxin units/mL). Patients received a light meal after the echocardiography at 60 minutes intradialysis. All patients were dialyzed in a supine position because this was the most convenient position for repeated intradialysis echocardiography.

Echocardiography Examination

Two-dimensional echocardiography was performed, including color flow mapping, blood pool, and tissue Doppler echocardiography. A dedicated team of experienced technicians, using a General Electric VIVID 7 system with a 2.5-mHz probe, recorded echocardiographic images. One experienced technician (Y.M.H.) performed all analyses off-line according to the guidelines of the European Society of Echocardiography[25]. At least 3 consecutive heartbeats in each view were acquired. Peak early (E) and late (A) diastolic filling velocities, deceleration time, and isovolemic relaxation time were measured at each time point. Tissue Doppler-derived early diastolic velocity (e') was measured on the lateral, septal, anterior, and inferior junction of the myocardium and mitral valve annulus. From these values, the average e' (mean e') value was calculated. Predialysis LV diastolic function was graded using the recent classification system by Nagueh et al[25]. LV mass index (LVMi) was calculated as described previously[26]. LVH was defined as LVMi >95 g/m2 for women and >115 g/m2 for men.

Statistical Analysis

Data are reported as mean ± standard deviation for continuous variables with normal distributions, median (interquartile range [IQR]) for skewed variables, and number (percentage) for categorical data. Comparisons of parameters with baseline were made by paired t test, Wilcoxon signed rank test, or χ^2 for variables with normal or skewed distributions and categorical variables, respectively. The overall change in time was analyzed using generalized estimating equation models. The association of blood volume change, ultrafiltration volume and rate, and BNP level with change in E and mean e' also was evaluated by generalized estimating equation models, with correction for age, sex, and predialysis LVMi and heart rate because LVH may impair diastolic filling[27,28] and heart rate determines the time that is available for diastolic filling[29,30]. For this analysis, BNP, E, and mean e' values were log-transformed. A 2-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed with STATA, version 11 (StataCorp LP), and SPSS, version 20 (SPSS Inc).

Results

Patient Characteristics

The recruitment process for participants is outlined in Fig 1. Of 159 patients who were eligible for this study, 50 did not give informed consent. These patients were less frequently men (48% vs 65%; p=0.04), had a longer dialysis vintage (median, 44.0 [IQR, 19-60] vs 21.7 [IQR, 8-49] months; p=0.008), and had a lower frequency of hypertension (44% vs 80%; p<0.001) in comparison to patients who participated in this study. Age, diabetes status, and proportion of patients with cardiovascular history did not differ significantly between eligible patients who did and did not participate in this study.

Characteristics of the 109 patients who participated in this study are listed in Table 1. Mean age was 62.5 ± 15.6 (SD) years and 65% were men. They had been treated with dialysis for a median of 21.7 (IQR, 8.0-48.5) months. Twenty-three percent of patients had diabetes and 80% had hypertension. Mean prescribed and clinical dry weights were 77.4 ± 15.2 and 78.0 ± 15.2 kg, respectively. Almost all our patients reached their prescribed dry weight after dialysis. Interdialytic weight gain was 2.3 ± 1.4 kg.

Blood Pressure, Heart Rate, and Clinical

Tolerability of Hemodialysis Average total ultrafiltration volume was 2.55 ± 0.78 L and mean ultrafiltration rate was 8.5 ± 2.6 mL/kg/h (Table 2). Blood volume decreased

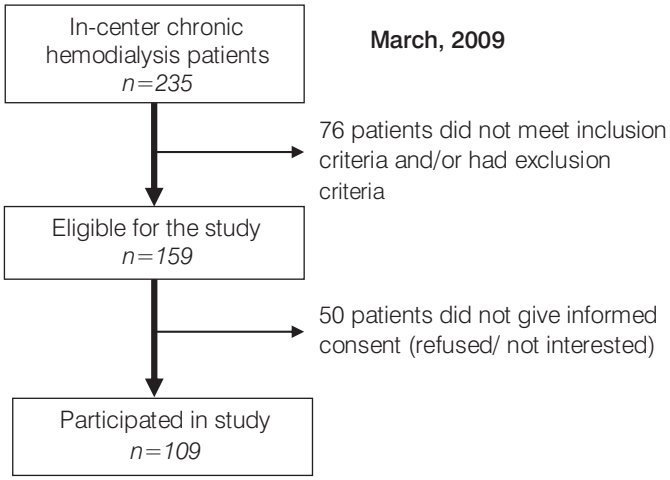

Figure 1 Recruitment process of study participants.

Table 1 Patient Characteristics.

Variable	Study population(n=109)
Age (y)	62.5 ± 15.6
Male sex	71 (65)
Dialysis vintage (mo)	21.7 [8.0-48.5]
Diabetes	25 (23)
Hypertension	87 (80)
Body mass index (kg/m^2)	25.9 ± 4.5
Cardiovascular history	25 (23)
LVMi (g/m^2)	93.3 ± 25.9
Primary renal disease	
Hypertension	18 (17)
Diabetes	14 (13)
ADPKD	14 (13)
FSGS	10 (9)
IgA nephropathy	4 (4)
Chronic pyelonephritis	3 (3)
Glomerulonephritis	13 (12)
Other	16 (15)
Unknown	17 (16)
Albumin (g/l)	39.1 ± 3.3
Weekly Kt/V	4.3 ± 0.7
Prescribed dry weight (kg)	77.4 ± 15.2
Clinical dry weight (kg)	78.0 ± 15.2
Interdialysis weight gain (kg)	2.3 ± 1.4

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range].
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; LVMi, left ventricular mass index.

significantly during dialysis (Table 2). Systolic and diastolic blood pressures decreased and heart rate increased significantly during dialysis (Table 2). None of the patients had angina or other symptoms during or after dialysis that raised clinical suspicion of myocardial ischemia.

Laboratory Measurements

Mean (±standard deviation) hematocrit and ionized calcium values increased and magnesium levels decreased significantly during dialysis (all $p<0.01$; Table 2). BNP levels did not change significantly during dialysis (Table 2).

Table 2 Measured Parameters Before, During, and After Hemodialysis.

	Predialysis	60 min intradialysis	180 min intradialysis	30 min postdialysis	*P*[a]
Ultrafiltration volume (L)	-	0.64 ± 0.19[b]	1.92 ± 0.58[b]	2.55 ± 0.78[b]	
Ultrafiltration rate (ml/kg/h)	-	8.5 ± 2.6	8.5 ± 2.6	8.5 ± 2.6	
Blood volume change (%)	-	-1.1 ± 3.8[b]	-3.8 ± 4.6[c]	-4.3 ± 5.2[c]	0.01
Systolic BP (mmHg)	140.3 ± 24.9	132.6 ± 23.6[b]	124.0 ± 28.8[c]	131.9 ±25.6[c]	<0.001
Diastolic BP (mmHg)	80.5 ± 16.7	73.4 ± 13.2[c]	70.6 ± 19.8[b]	73.4 ± 14.2[c]	<0.001
Heart rate (beats/min)	73 (63-82)	74 (66-85)	76.5 (69-87)[b]	79 (68-87)[c]	0.05
Hematocrit	34.9 ± 3.8	35.5 ± 3.7[b]	36.3 ± 4.1[c]	36.5 ± 4.2[c]	0.01
Ionized calcium (mmol/L)	1.21 ± 0.09	1.24 ± 0.06[c]	1.24 ± 0.05[c]	1.25 ± 0.05[c]	<0.001
Magnesium (mmol/L)	1.07 ± 0.18	0.93 ± 0.12[c]	0.89 ± 0.08[c]	0.87 ± 0.07[c]	<0.001
BNP (ng/L)	337[161-736]	293[162-677][b]	277[145-630][c]	278[148-626][c]	0.6

Note: N =109. Values are given as mean ± standard deviation or median [interquartile range].
Abbreviations: BNP, brain natriuretic peptide; BP, blood pressure.
[a]P value for the overall change (generalized estimating equations).
[b]p< 0.01, [c]p<0.001.

Echocardiographic Parameters

Mean LVMi was 93.3 ± 25.9 g/m2. None of the patients had pericardial effusion. A total of 11 patients had significant (grades 2-3) mitral valve insufficiency and one patient had mitral valve stenosis. According to the Nagueh classification of LV diastolic function, only 29% of patients had normal predialysis diastolic function (grade 0). Grades 1, 2, and 3 diastolic dysfunction were observed in 14%, 45%, and 12% of patients, respectively. As listed in Table 3, E values decreased early during dialysis. At 60 minutes intradialysis, E had decreased 21.4% ± 17.6% compared with predialysis ($p<0.001$). At 180 minutes intradialysis, E had decreased further by 30.5% ± 19.2% compared with predialysis ($p<0.001$). At 30 minutes postdialysis, E had partially recovered and was just 20.0% ± 17.0% lower than predialysis, although this difference was still statistically significant ($p<0.001$). The E:A ratio decreased and deceleration time and isovolemic relaxation time increased significantly during hemodialysis (all $p<0.001$), with the most prominent changes occurring within the first 60 minutes of dialysis.

Tissue Doppler-derived mean e' decreased early during dialysis (Table 3). At 60 minutes intradialysis, mean e' had decreased 16.0% ± 18.6% compared with predialysis ($p<0.001$). At 180 minutes intradialysis, mean e' had decreased further 19.5% ± 21.8% compared with predialysis. At 30 minutes postdialysis, mean e' had partially recovered but was still 12.3% ± 21.1% lower than the predialysis value ($p<0.001$). E:e' decreased significantly at 60 minutes intradialysis ($p<0.001$) and was stable during the rest of the dialysis session (Table 3). There was no difference in the course of E and mean e' values between patients with and without significant mitral valve disease (data not shown).

Figure 2 shows changes in E and mean e' in relation to the change in blood volume. The steepest decreases in E and mean e' values occurred from predialysis to 60 minutes intradialysis, whereas the most prominent decline in blood volume occurred at 180 minutes intradialysis and at the end of the dialysis session.

Association Between Volume Parameters and Change

In Diastolic Function Parameters Both change in blood volume and BNP level were associated significantly with change in E at 60 and 180 minutes intradialysis (Table 4). This association remained significant after adjustment for age, sex, LVMi, and heart rate. Ultrafiltration volume and rate were not associated significantly with change in E values at any time during dialysis in unadjusted analyses. After adjustment for age, sex, LVMi, and heart rate, ultrafiltration volume was associated significantly with change in E values at 180 minutes intradialysis (Table 4).

The change in tissue Doppler-derived mean e' was not associated with any volume parameters at either 60 or 180 minutes intradialysis (Table 5) in unadjusted analyses. Adjustment for age, sex, LVMi, and heart rate did not change these

Table 3 Echocardiographic Parameters Before, During, and After Hemodialysis.

	Predialysis	60 min intradialysis	180 min intradialysis	30 min postdialysis	*P*[a]
E (m/s)	0.93 ± 0.24	0.71 ± 0.22[b]	0.63 ±0.20[b]	0.73 ± 0.23[b]	<0.001
A (m/s)	0.86 ± 0.24	0.82 ± 0.21[c]	0.80 ± 0.22[b]	0.84 ± 0.23	0.001
E:A	1.11 ± 0.34	0.88 ± 0.28[b]	0.82 ± 0.37[b]	0.88 ± 0.28[b]	<0.001
DT (s)	224 ± 83	258 ± 86[b]	282 ± 94[b]	253 ± 70[b]	<0.001
IVRT (s)	94 ± 25	115 ± 33[b]	112 ± 35[b]	107 ± 31[b]	<0.001
Mean e' (cm/s)	6.6 ± 2.1	5.6 ± 2.2[b]	5.3 ± 2.0[b]	5.8 ± 2.0[b]	<0.001
E:e'	15.1 ± 5.6	14.3 ± 7.1[d]	13.6 ± 7.3[b]	14.0 ± 6.9[b]	<0.001

Abbreviations: A, mitral late inflow velocity; DT, deceleration time; E, mitral early inflow velocity; e', tissue Doppler early diastolic flow; IVRT, isovolemic relaxation time.
[a]P value for the overall change (generalized estimating equations).
[b]$p<0.001$, [c]$p<0.05$, [d]$p<0.01$ in comparison with predialysis.

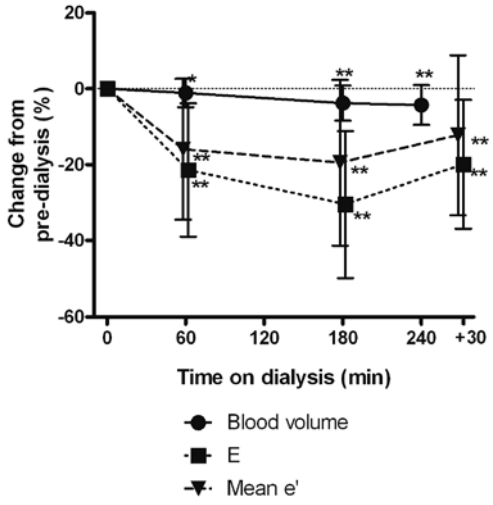

Figure 2 Changes in blood volume, mitral early inflow (E), and mean tissue Doppler early diastolic velocity (e') in comparison to predialysis values.

The lines and error bars depict mean and standard deviation for the 109 patients. Duration of hemodialysis was 240 minutes; 30 indicates the 30-minute postdialysis echocardiography. *p<0.05 and **p<0.01 in comparison to predialysis values.

associations, except for BNP level, which was associated significantly with change in mean e' at 180 minutes intradialysis.

Table 4 Multivariate Longitudinal Analysis of Associations Between Change in Mitral Early Inflow Velocity (E) and Change in Measured Parameters.

	60 min intradialysis		180 min intradialysis	
	β (95% CI)	*P*	β (95% CI)	*P*
Blood volume change (%)				
Model 1[a]	0.006 (0.001-0.011)	0.02	0.007 (0.003-0.01)	<0.001
Model 2[b]	0.006 (0.001-0.011)	0.02	0.007 (0.003-0.01)	<0.001
Model 3[c]	0.007 (0.001-0.012)	0.01	0.007 (0.003-0.01)	0.001
Ultrafiltration volume (L)				
Model 1[a]	-0.04 (-0.13-0.05)	0.4	-0.02 (-0.06-0.01)	0.2
Model 2[b]	-0.06 (-0.15-0.04)	0.2	-0.03 (-0.06-0.01)	0.1
Model 3[c]	-0.07 (-0.18-0.05)	0.2	-0.01 (-0.06-0.03)	0.6
Ultrafiltration rate (ml/kg/h)				
Model 1[a]	-0.007 (-0.039-0.025)	0.7	-0.006 (-0.02-0.006)	0.3
Model 2[b]	-0.01 (-0.04-0.02)	0.6	-0.007 (-0.02-0.005)	0.3
Model 3[c]	-0.01 (-0.05-0.03)	0.5	-0.01 (-0.03-0.00)	0.06
Log BNP level				
Model 1[a]	0.02 (-0.001-0.03)	0.06	0.03 (0.005-0.05)	0.02
Model 2[b]	0.02 (0.002-0.04)	0.03	0.03 (0.008-0.06)	0.009
Model 3[c]	0.02 (0.002-0.04)	0.03	0.03 (0.003-0.06)	0.03

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval.
[a]No adjustment. [b]Adjusted for age and sex. [c]Adjusted for age, sex, left ventricular mass index, and heart rate.

Table 5 Multivariate Longitudinal Analysis of Associations Between Change in Tissue Doppler Early Diastolic Velocity (mean e') and Change in Measured Parameters.

	60 min intradialysis		180 min intradialysis	
	β (95% CI)	*P*	β (95% CI)	*P*
Blood volume change (%)				
Model 1[a]	0.002 (-0.003-0.007)	0.4	0.004 (-0.001-0.008)	0.09
Model 2[b]	0.002 (-0.003-0.007)	0.4	0.004 (0.00-0.008)	0.08
Model 3[c]	0.004 (-0.001-0.009)	0.2	-0.003 (-0.009-0.003)	0.3
Ultrafiltration volume (L)				
Model 1[a]	0.003 (-0.09-0.10)	0.9	-0.01 (-0.05-0.03)	0.7
Model 2[b]	-0.01 (-0.11-0.09)	0.8	-0.01 (-0.05-0.02)	0.5
Model 3[c]	-0.02 (-0.14-0.10)	0.8	-0.001 (-0.002-0.001)	0.9
Ultrafiltration rate (mL/kg/h)				
Model 1[a]	-0.001 (-0.04-0.04)	0.9	0.001 (-0.01-0.02)	0.9
Model 2[b]	-0.004 (-0.04-0.03)	0.8	0.00 (-0.01-0.02)	0.9
Model 3[c]	-0.005 (-0.05-0.03)	0.8	0.01 (-0.008-0.03)	0.3
Log BNP level				
Model 1[a]	0.01 (-0.01-0.03)	0.2	0.02 (-0.002-0.04)	0.07
Model 2[b]	0.02 (-0.01-0.04)	0.1	0.02 (-0.001-0.05)	0.06
Model 3[c]	0.02 (-0.001-0.04)	0.06	0.04 (0.01-0.06)	0.01

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval.
[a]No adjustment. [b]Adjusted for age and sex. [c]Adjusted for age, sex, left ventricular mass index, and heart rate.

Discussion

In this study, we evaluated the acute effects of hemodialysis on LV diastolic function. The main finding is that diastolic function worsened significantly even early (at 60 minutes) in the hemodialysis session.

Previous studies have exclusively assessed diastolic function before and after hemodialysis[19-22]. The present study confirms the results of these studies and additionally shows that the worsening of diastolic function during hemodialysis is even worse than is captured when only pre- and postdialysis echocardiography are being performed. The early studies used conventional mitral valve inflow diastolic parameters such as E and E:A to evaluate the effect of hemodialysis on diastolic function[19,20.] Subsequent studies demonstrated that the less preload-dependent diastolic function parameter tissue Doppler velocity (mean e') also decreases from pre- to posthemodialysis[21-23]. The present study shows that hemodialysis acutely affects both mitral valve inflow and tissue Doppler velocities. These 2 parameters follow a similar time course, with the steepest changes in the first hour of hemodialysis.

Because echocardiographic parameters of diastolic function are known to be volume dependent, most groups have attributed the change in diastolic function parameters during hemodialysis to hypovolemia as a result of ultrafiltration. However, none of these studies has evaluated diastolic function parameters in relation to volume parameters. Our study shows that there are significant associations between change in mitral early inflow (E) and several volume indexes at 60 and 180 minutes intradialysis. This is not unexpected because the decrease in blood volume probably is sufficient to affect ventricular filling by a reduction in preload. However, we did not find a significant association between changes in tissue Doppler-derived e' and volume indexes during dialysis, except for BNP level at 180 minutes intradialysis, after adjustment for age, sex, LVMi, and heart rate. Additionally, although tissue Doppler-derived velocity mean e' values continued to decrease between 60 and 180 minutes intradialysis, the steepest decrease in mean e' was observed during the first 60 minutes. Finally, the course of mean e' values did not mirror the change in blood volume. These findings certainly do not exclude a role of hypovolemia in the decline of tissue Doppler-derived velocity mean e' because of the limitations that are inherent to the measurement of relative blood volume[31]. First, relative blood volume changes may not fully reflect central blood volume changes,[32] and, second, relative blood volume changes do not capture the hypovolemic effect of blood loss to the extracorporal circuit (in this study, 200 mL). At the same time, our observations raise the possibility that volume changes may not be the dominant factor in the early decrease in tissue Doppler velocity mean e' values during hemodialysis.

Various non–volume-related mechanisms could cause impairment of LV relaxation and consequently a reduction in LV diastolic filling. Notably, these factors are not

mutually exclusive and different mechanisms may be involved at varying times during hemodialysis. First, LVH may contribute to diastolic dysfunction because it opposes LV diastolic filling[27,28]. Second, reductions in blood pressure[30] and increases in heart rate[29] may affect diastolic filling. Third, changes in plasma calcium and magnesium concentrations may influence LV relaxation[33,34]. Fourth, hemodialysis-induced myocardial ischemia may cause impaired LV relaxation and thus diastolic dysfunction. We and others have previously shown that hemodialysis induces a pronounced reduction in myocardial blood flow[9,10]. Interestingly, it has been reported that myocardial blood flow already decreased significantly within 30 minutes after the start of hemodialysis before the start of ultrafiltration[10]. Studies that evaluate the effect of hemodialysis on diastolic function in relation to changes in myocardial perfusion may elucidate whether myocardial ischemia is involved in the early worsening of hemodialysis-induced diastolic function.

The observation that diastolic function worsens during hemodialysis adds to the increasing evidence that conventional hemodialysis is associated with acute cardiac stress[5,11]. Repetitive hemodialysis- induced cardiac stress may have cumulative adverse effects on cardiac function that lead to cardiac failure and eventually death. It has been shown that hemodialysis-induced LV systolic dysfunction predisposes for progressive decline in LV systolic function[4]. At present, it is not known whether worsening of diastolic function during hemodialysis also predisposes for progression of diastolic dysfunction over time.

A limitation of this study is that the measurement of relative blood volume may be influenced by various factors, such as changes in posture and food intake during hemodialysis,[31] although posture (supine) and food intake (light meal) were standardized in this study. Additionally, the change in blood volume may underestimate the change in absolute blood volume[32]. However, we have previously shown by direct measurement of absolute blood volume that the change in absolute blood volume paralleled the relative blood volume change in the first hour of hemodialysis[32]. This still does not exclude the possibility that changes in relative blood volume do not mirror central blood volume changes. Additionally, relative blood volume changes do not capture the hypovolemic effect of the transition of blood to the extracorporal system, as discussed. Future studies should measure the change in diastolic function during hemodialysis in relation to central blood volume. A second limitation of this study is that we did not perform echocardiography at the nadir of the blood volume decline, which is usually reached at the very end of the hemodialysis session (at 240 minutes), but instead, at 180 minutes into the session. A third limitation is the lack of measurement of left atrial volume for the evaluation of diastolic function. Fourth, the observed differences in patient characteristics between eligible patients who participated and those who did not participate in the study potentially limit the generalizability of our results. Finally, our results may not be generalizable to dialysis patients who are treated with higher ultrafiltration rates.

In conclusion, LV diastolic function worsens early during hemodialysis. The early decrease in tissue Doppler-derived mean e' was unrelated to the change in relative blood volume. Although this does not exclude a role of hypovolemia because of the limitations of relative blood volume measurement, it raises the possibility that non–volume-related mechanisms are involved in the early decrease in tissue Doppler velocity mean e' during hemodialysis.

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Chapter 6

Hemodialysis-Induced Regional Left Ventricular Systolic Dysfunction and Inflammation: A Cross-sectional Study

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Abstract

Background: Hemodialysis may acutely induce regional left ventricular (LV) systolic dysfunction, which is associated with increased mortality and progressive heart failure. We tested the hypothesis that hemodialysis-induced regional LV systolic dysfunction is associated with inflammation and endothelial injury. Additionally, we studied whether hemodialysis-induced LV systolic dysfunction is associated with an exaggerated bioincompatibility reaction to hemodialysis.

Study Design: Cross-sectional study.

Setting & Participants: 105 hemodialysis patients on a thrice-weekly dialysis schedule were studied between March 2009 and March 2010. Predictors: Plasma indexes of inflammation (high-sensitivity C-reactive protein, pentraxin 3 [PTX3], interleukin 6 [IL-6], and IL-6:IL-10 ratio), bioincompatibility (leukocytes, neutrophils, complement C3, and myeloperoxidase), and endothelial function (soluble intercellular adhesion molecule 1 [ICAM-1], von Willebrand factor, proendothelin, and endothelin) were measured just before dialysis and at 60, 180, and 240 minutes intradialysis.

Outcomes: Hemodialysis-induced regional LV systolic function. Wall motion score was measured by echocardiography at 30 minutes predialysis, 60 and 180 minutes intradialysis, and 30 minutes postdialysis. We defined hemodialysis-induced regional LV systolic dysfunction as an increase in wall motion score in 2 or more segments.

Results: Patients with hemodialysis-induced regional LV systolic dysfunction (n=29 [27%]) had significantly higher predialysis high-sensitivity C-reactive protein, PTX3, IL-6, and IL-6:IL-10 ratio values. Predialysis levels of bioincompatibility and endothelial markers did not differ between groups. Intradialysis courses of markers of inflammation, bioincompatibility, and endothelial function did not differ in patients with versus without hemodialysis-induced regional LV systolic dysfunction.

Limitations: Coronary angiography or computed tomography for quantification of coronary calcifications in our patients was not performed; therefore, we could not relate markers of inflammation to the extent of atherosclerosis.

Conclusions: Patients with hemodialysis-induced regional LV systolic dysfunction have a proinflammatory cytokine profile. There was no indication of an association with an exaggerated bioincompatibility reaction to hemodialysis.

Introduction

Hemodialysis is life-saving in patients requiring replacement of kidney function, but the adverse effects of the hemodialysis procedure may contribute to the high cardiovascular risk observed in these patients. The hemodialysis procedure clearly is stressful for the cardiovascular system because it often is accompanied by hemodynamic instability[1]. We and other investigators have shown that regular hemodialysis sessions can induce reversible reductions in myocardial blood flow, with such severity as to lead to transient left ventricular (LV) systolic dysfunction[2,3]. Subsequent studies have shown that hemodialysis-induced LV systolic dysfunction is relatively frequent and is associated with an increased incidence of all-cause mortality and progressive heart failure[4,5]. The pathogenesis of hemodialysis-induced LV systolic dysfunction currently is unknown. In the general population, acute and chronic cardiac ischemia and heart failure are all associated with a proinflammatory cytokine pattern, and inflammation is thought to play a pivotal role in the progression of these conditions[6]. Hemodialysis patients have markedly elevated levels of various proinflammatory cytokines, and higher levels of these inflammatory markers are associated with increased risk of cardiovascular events and mortality[7]. We hypothesized that systemic inflammation also has a role in the pathophysiology of hemodialysis-induced regional LV systolic dysfunction, for example, by its negative effects on endothelial function of the myocardial microcirculation and/or by cardiodepressive effects of proinflammatory cytokines[8,9]. The first objective of this study therefore was to evaluate whether patients with hemodialysis-induced regional LV systolic dysfunction have elevated predialysis plasma levels of markers of inflammation and endothelial injury. The second objective was to investigate whether patients with hemodialysis-induced regional LV systolic dysfunction have an exaggerated bioincompatibility response to hemodialysis as a potential source of systemic inflammation.

Methods

Patients and Study Design

Hemodialysis patients from the Dialysis Center Groningen and University Medical Center Groningen were eligible for this study if they were treated with hemodialysis for more than 3 months and were on a thrice-weekly hemodialysis schedule. Patients with severe heart failure (New York Heart Association class IV) and patients who did not have an adequate window for transthoracic echocardiography imaging were excluded. The recruitment process of participants is outlined in Fig 1. Of the 235 in-center patients during the study period, 76 patients were not eligible for the study. Of these, 41 patients did not fulfill inclusion criteria, 27 patients were excluded due to

severe heart failure, and 8 patients were excluded due to lack of a proper window for echocardiographic imaging.

Patients were studied at the dialysis session following the longest interdialytic interval (3 days). Dialysis session length was 4 hours. Patients' characteristics were assessed at study entry. Diabetes was defined as fasting blood glucose level ≥ 7 mmol/L or use of antidiabetic drugs. Hypertension was defined as predialysis systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg or use of antihypertensive drugs. Cardiovascular history was defined as a history of ischemic heart disease, congestive heart failure, coronary artery bypass grafting, percutaneous coronary intervention, stroke, or peripheral vascular disease. These data were obtained from patients' medical records.

Blood pressure and heart rate were measured before and after dialysis. Ultrafiltration rate was expressed in milliliters per hour per kilogram by dividing ultrafiltration volume by dialysis session length and target weight[10]. Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentrations according to the second-generation logarithmic Daugirdas equation[11]. Nutritional status was assessed with the 7-point subjective global assessment[12]. Patients with subjective global

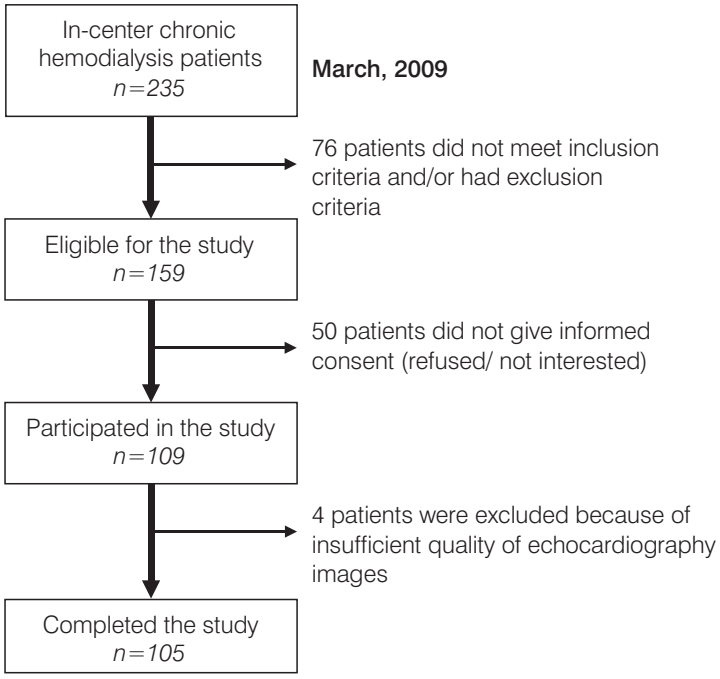

Figure 1 Recruitment process of study participants.

assessment score of 5 or lower were defined as malnourished. The study was performed according to the Declaration of Helsinki and was approved by the Medical Ethical Committee of the University Medical Center Groningen. All patients gave written informed consent. The study was performed between March 2009 and March 2010.

Dialysis Settings

All patients were on bicarbonate dialysis with a low-flux polysulfone hollow-fiber dialyzer (F8; Fresenius Medical Care). Blood flow and dialysate flow rates were 250-350 and 500 mL/min, respectively. Dialysate temperature was 36 ^{o}C in all patients. Dialysate composition was as follows: sodium, 139 mmol/L; calcium, 1.5 mmol/L; magnesium, 0.5 mmol/L; chloride, 108 mmol/L; bicarbonate, 34 mmol/L; acetate, 3.0 mmol/L; and glucose, 1.0 g/L. Potassium concentration was 1.0 or 2.0 mmol/L, depending on prevailing plasma potassium concentrations. We used constant ultrafiltration rate and dialysate conductivity. The water for hemodialysis complied with the requirements of the European Pharmacopoeia (<100 colony-forming units/mL; <0.25 endotoxin units/ mL). Patients received a light meal after the echocardiography at 60 minutes intradialysis. Patients received dialysis in a supine position, which was convenient for echocardiography and excluded the effect of posture changes on blood volume.

Echocardiography Examination

A team of 3 experienced technicians performed 2-dimensional echocardiography using a General Electric VIVID 7 system with a 2.5-mHz probe. Echocardiography was performed 4 times: before hemodialysis, at 60 and 180 minutes intradialysis, and 30 minutes postdialysis. Global and regional systolic function was evaluated by LV ejection fraction (LVEF) and wall motion score index (WMSI), respectively. LVEF was calculated using the biplane Simpson method. WMSI was evaluated according to the 16-segment model as recommended by the European Society of Echocardiography[13] by a single technician (Y.M.H.) who was blinded to the order of echocardiography studies. For each patient, the number of LV regions that developed new regional wall motion abnormalities during hemodialysis was calculated. Regional wall motion abnormality was defined as an increase in wall motion score in that specific LV segment occurring at either 60 or 180 minutes intradialysis or 30 minutes posthemodialysis in comparison to predialysis. Hemodialysis-induced regional LV systolic dysfunction was defined as the development of new regional wall motion abnormalities in 2 or more LV segments compared with predialysis.

LV mass index was calculated as described previously[14]. LV hypertrophy was defined as LV mass index >95 g/m2 for women and >115 g/m2 for men.

Laboratory Procedures

Blood samples were collected from the arterial line of the dialysis circuit at the start of hemodialysis, 60 and 180 minutes intradialysis, and the end of dialysis. Hematocrit, leukocytes, neutrophils, albumin, calcium, and phosphate values were determined immediately. For determination of cytokine levels, blood was centrifuged within 30 minutes of collection at 3,500 rpm for 15 minutes. Supernatants were stored at -80°C until measurement. Prior to assay, samples were thawed and recentrifuged. Samples were analyzed at a single time to eliminate interassay variability. Laboratory personnel were unaware of patient data or outcome.

Inflammatory Markers

High-sensitivity C-reactive protein (hs-CRP) was measured with the N latex CRP monoassay (Siemens Healthcare Diagnostics). Pentraxin 3 (PTX3), interleukin 6 (IL-6), and IL-10 were measured by quantitative sandwich enzyme immunoassay technique (R&D Systems Inc). PTX3 was measured because it responds rapidly to inflammatory stimuli and is considered an appropriate marker for investigating inflammatory reactions that may occur during single dialysis sessions[15]. Tumor necrosis factor α (TNF-α) was measured by Quantikine HS Human Immunoassay (R&D Systems Inc).

Bioincompatibility Markers

Myeloperoxidase, which reflects leukocyte activation in the extracorporal system, was measured by enzyme-linked immunosorbent assay (HyTest Ltd). Complement factor C3 (C3) was measured in EDTA plasma using a nephelometric assay (Siemens Healthcare Diagnostics) on the BNII Nephelometer system (Siemens Healthcare Diagnostics).

Endothelial Markers

Soluble intercellular adhesion molecule 1 (ICAM-1) was measured by quantitative sandwich enzyme immunoassay technique (R&D Systems Inc). von Willebrand factor was measured by enzyme-linked immunosorbent assay (Dakopatts). Measurement of endothelin was based on competition with surface-bound recombinant endothelin (RayBiotech Inc) for binding to a specific antibody (RayBiotech Inc). The amount of captured antibody was measured by substrate conversion of a horseradish peroxidase-labeled secondary antibody. Proendothelin was measured by novel sandwich fluoroimmunoassay (B.R.A.H.M.S) using the automated system B.R.A.H.M.S KRYPTOR. Concentrations of all biomarkers measured during and after dialysis were corrected for the effect of hemoconcentration according to Schneditz et al[16].

Statistical Analyses

Data are reported as mean $\pm$ standard deviation for continuous variables with normal distributions, median and interquartile range for skewed variables, and number and

percentage for categorical data. Differences in predialysis levels of biomarkers between patients with and without hemodialysis-induced regional LV systolic dysfunction were evaluated by t test for normally distributed and Wilcoxon signed rank test for skewed parameters. Univariate and multivariate logistic regression models were computed to evaluate the association between predialysis levels of biomarkers and the occurrence of hemodialysis-induced regional LV systolic dysfunction. Multivariate models were adjusted for age, sex, dialysis vintage, and predialysis LV systolic function (WMSI). For these analyses, cytokine concentrations were log-transformed. Backward stepwise logistic regression was used to find the best model with a combination of inflammatory markers that predicted the occurrence of hemodialysis-induced regional LV systolic dysfunction. The nonparametric test for trend (nptrend in Stata) was used to evaluate the relation between predialysis biomarker levels and number of LV segments that developed regional wall motion abnormalities during or after hemodialysis.

The possible significance of the overall intradialysis change in biomarker levels during hemodialysis was evaluated by generalized estimating equations (GEEs). Intradialysis levels of these parameters at each individual time (60, 180, and 240 minutes intradialysis) also were compared with predialysis levels using paired t test for normally distributed and signed rank test for skewed parameters. Differences in the intradialysis course of these parameters between patients with and without hemodialysisinduced regional LV systolic dysfunction were evaluated using GEEs with adjustment for predialysis values. Skewed values were log-transformed before performing GEE models. Two-sided $p<0.05$ was considered statistically significant. Statistical analyses were performed with SPSS, version 20 (SPSS Inc), and Stata, version 11 (StataCorp LP).

Results

Patient Characteristics

Characteristics of the 105 patients eligible for analyses are shown in Table 1. Twenty-nine patients (27%) developed hemodialysis-induced regional LV systolic dysfunction. The median age of these patients was 66 (interquartile range, 51-75) years and did not differ significantly compared with patients who did not develop systolic dysfunction ($p=0.2$). Among patients that developed hemodialysis-induced regional LV systolic dysfunction, the proportion of men was higher compared with patients who did not develop systolic dysfunction ($p=0.05$). The proportion of patients with malnutrition was not significantly different between the 2 groups ($p=0.5$). Patients with hemodialysis-induced regional LV systolic dysfunction had a higher LV mass index ($p=0.05$). However, when men and women were analyzed separately, there

Table 1 Patient characteristics.

	All patients (N=105)	No HD induced Regional LVSD (n=76)	HD-Induced Regional LVSD (n=29)	*P*
Age (y)	66 [51-75]	64 [50-75]	69 [58-78]	0.2
Male sex	68 (64.8)	45 (59.2)	23 (79.3)	0.05
Dialysis vintage (mo)	21.4 [7.8-48.5]	24 [8.3-48.3]	18.4 [5.5-49.7]	0.7
Diabetes	23 (21.9)	19 (25.0)	4 (13.8)	0.3
Hypertension	84 (80.0)	61 (80.3)	23 (79.3)	0.9
History of cardiovascular disease	23 (21.9)	15 (19.7)	8 (27.6)	0.4
BMI (kg/m^2)	25.2 [23.0-28.1]	25.2 [22.6-28.3]	25.2 [23.2-27.8]	0.9
Primary renal disease				
Hypertension	17 (16.2)	12 (15.8)	5 (17.2)	0.9
Diabetes	13 (12.4)	11 (14.5)	2 (6.9)	0.3
ADPKD	14 (13.3)	10 (13.6)	4 (13.8)	0.9
FSGS	10 (9.5)	8 (10.5)	2 (6.9)	0.6
IgA nephropathy	4 (3.8)	4 (5.3)	0 (0)	0.2
Chronic pyelonephritis	1 (1.0)	1 (1.3)	0 (0)	0.5
Glomerulonephritis	13 (12.4)	10 (13.2)	3 (10.3)	0.7
Other diagnoses	16 (15.2)	10 (13.2)	6 (20.6)	0.2
Unknown	17 (16.2)	10 (13.2)	7 (24.1)	0.2
Medication				
Aspirin	57 (54.3)	46 (60.5)	11 (37.9)	0.04
CCB	14 (13.3)	12 (15.8)	2 (6.9)	0.2
β-Blocker	60 (57.1)	45 (59.2)	15 (51.7)	0.5
ACE inhibitor	10 (9.5)	8 (10.5)	2 (6.9)	0.6
ARB	14 (13.3)	10 (13.2)	4 (13.8)	0.3
Statin	20 (19.1)	14 (18.4)	6 (20.7)	0.8
Malnourished	22 (21)	15 (20)	7 (24)	0.5
Hematocrit (%)	35.0±3.7	35.1±4.0	34.6±3.0	0.5
Albumin (g/l)	39 [37-41]	39 [37-42]	39 [37-41]	0.6

Calcium (mmol/l)	2.33±0.16	2.33±0.17	2.33±0.14	0.9
Phosphate (mmol/l)	1.7 [1.3-1.9]	1.7 [1.3-2.0]	1.6 [1.4-1.9]	0.9
Kt/V	4.3 [3.8-4.7]	4.3 [3.8-4.7]	4.0 [3.9-4.5]	0.4
Ultrafiltration volume (L)	2.6±0.8	2.5±0.7	2.60±0.9	0.8
Ultrafiltration rate (ml/kg/h)	8.5±2.6	8.6±2.5	8.3±3.0	0.6
Systolic blood pressure				
Predialysis (mmHg)	140.5±25.2	143.4±25.0	132.9±21.7	0.06
Postdialysis (mmHg)	132.4±25.7	134.6±26.6	126.6±22.7	0.2
Heart rate				
Predialysis (beats/min)	72 [63-83]	71 [63–82]	74 [66–86]	0.3
Postdialysis (beats/min)	79 [67-87]	77 [66–86]	84 [77–93]	0.06
LV mass index (g/m^2)	93.3±26.0	89.9±24.6	101.7±27.9	0.05
Male	98.1±25.8	94.5±23.3	104.5±29.2	0.7
Female	84.7±24.4	83.9±25.4	89.3±19.1	0.2
LV hypertrophy	25 (23.8)	19 (25)	6 (20.7)	0.6
Male	14 (13.3)	9 (11.8)	5 (17.2)	0.9
Female	11 (10.5)	10 (13.2)	1 (0.04)	0.4
Predialysis LVEF, %	50.0±10.4	51.8±9.5	45.3±10.4	0.008
Predialysis WMSI, (median, IQR)	1.00 (1.00–1.13)	1.00 (1.00–1.03)	1.21 (1.06–1.44)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range].
Abbreviations: ACE, angiotensin-converting enzyme; ADPKD, adult dominant polycystic kidney disease; ARB, angiotensin receptorblocker; BMI, body mass index; CCB, calcium channel blocker; FSGS, focal segmental glomerulosclerosis; HD, hemodialysis; IgA, immunoglobulin A; LV, left ventricular; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; WMSI, wall motion score index.

was no significant difference between the 2 groups. Patients with hemodialysis-induced regional LV systolic dysfunction had worse predialysis systolic function ($p<0.001$ for WMSI; $p=0.008$ for LVEF). Ultrafiltration volume, ultrafiltration rate, blood pressure, heart rate (Table 1), and blood volume course (Fig 2) did not differ significantly between the 2 groups.

Predialysis Biomarker Concentrations

Predialysis values for hs-CRP ($P=0.01$), PTX3 ($P= 0.04$), IL-6 ($P=0.02$), and IL-6:IL-10 ratio ($p=0.002$) were significantly higher in patients with hemodialysis-induced regional LV systolic dysfunction (Table 2). Total leukocyte counts, neutrophil concentrations, and plasma TNF-α and IL-10 levels did not differ significantly between the 2 groups (all $p>0.05$). Predialysis levels of myeloperoxidase, C3, and endothelial markers also were not significantly different between the 2 groups (all $p>0.05$). von Willebrand factor levels tended to be significantly higher in patients with hemodialysis-induced regional LV dysfunction ($p=0.07$).

Patients with abnormal WMSI (WMSI>1) had significantly higher predialysis hs-CRP levels and tended to have higher IL-6 levels. Patients with abnormal LVEF (LVEF<50%) had significantly higher predialysis PTX3 and IL-6 levels and lower IL-10 levels and tended to have higher hs-CRP levels. There was no significant difference in levels of bioincompatibility and endothelial markers between patients with normal and abnormal WMSI and between patients with normal and abnormal LVEF (Table S1, available as supplementary material).

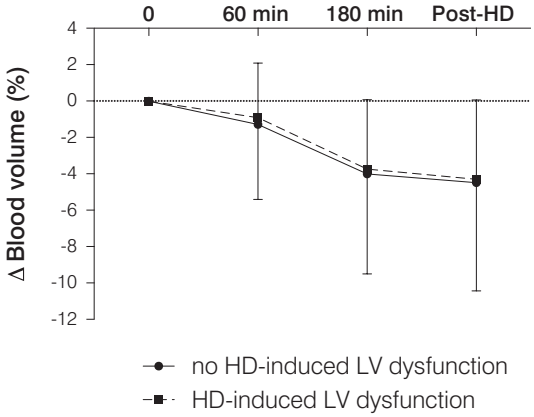

Figure 2 The course of blood volume in patients with and without hemodialysis (HD)-induced regional left ventricular (LV) systolic dysfunction (mean 6 standard deviation).

In univariate regression analysis, higher predialysis hs-CRP and PTX3 levels and higher IL-6/IL-10 ratios were associated significantly with the occurrence of hemodialysis-induced regional LV systolic dysfunction (Table 3). Higher IL-6 and lower IL-10 levels did not have statistically significant associations, but P values were 0.08 and 0.09, respectively. In multivariate analysis, higher hs-CRP, lower IL-10, and higher IL-6/IL-10 ratio values remained independently associated significantly with hemodialysis-induced regional LV systolic dysfunction after adjustment for age, sex, dialysis vintage, and predialysis WMSI (Table 3). For bioincompatibility and endothelial markers, none of the tests for association with hemodialysis-induced regional LV systolic dysfunction in multivariate analysis gave statistically significant results, although the P value for higher predialysis C3 levels was borderline ($p=0.07$; Table 3).

In a backward stepwise logistic regression model including the combination of all inflammatory markers, hs-CRP and IL-10 remained the most predictive inflammatory markers for the occurrence of hemodialysis-induced regional LV dysfunction, with hazard ratios of 4.36 and 0.16, respectively (Table S2).

Predialysis hs-CRP and IL-6:IL-10 ratio values showed a dose-effect pattern, with higher levels in patients developing an increasing number of regional wall motion abnormalities during or after hemodialysis ($P=0.01$ and $P=0.006$, respectively; Fig 3). Of the other markers of inflammation, IL-6 level did not have a statistically significant association, but $p=0.06$ (data not shown).

Changes in Biomarker Concentrations During Hemodialysis

In the entire group, PTX3, TNF-α, and IL-10 levels increased significantly, whereas leukocyte, neutrophil, C3, and IL-6:IL-10 ratio values decreased significantly during hemodialysis. hs-CRP levels did not change significantly when pre- and postdialysis values were compared ($p = 0.1$). Myeloperoxidase levels increased significantly ($p<0.001$) during dialysis, with a sharp increase at 60 minutes intradialysis ($p<0.001$; Table S3).

The intradialysis course of von Willebrand factor levels showed a peak at 60 minutes intradialysis, which was significantly higher compared with predialysis ($p<0.001$). Soluble ICAM-1 and endothelin levels increased significantly ($p< 0.001$), whereas proendothelin levels decreased significantly ($p<0.001$) during dialysis (Table S3).

Courses of levels of the inflammatory, bioincompatibility, and endothelial markers during hemodialysis did not differ significantly in patients with versus without hemodialysis-induced regional LV systolic dysfunction (all $p>0.05$; Table 2).

Table 2 Biomarker Concentrations in Patients With and Without HD-Induced regional LVSD.

	Predialysis	60 min intradialysis	180 min intradialysis	240 min intradialysis	*P*[a]
Inflammatory markers					
hsCRP (mg/L)[b]					
No HD-induced LVSD	4.4±3.7	4.4±3.3	4.4±3.3	4.5±3.3	0.7
HD-induced LVSD	8.0±2.4	7.7±2.8	8.6±2.5	8.3±2.5	
PTX3 (ng/ml)					
No HD-induced LVSD	2.57 (1.62-3.72)	3.43 (2.59-5.15)	3.77 (2.78-5.73)	3.97 (3.00-5.71)	0.09
HD-induced LVSD	3.05 (1.64-4.25)[c]	3.86 (2.26-6.05)	4.32 (2.68-6.93)	4.51 (2.97-8.15)	
TNF-α (pg/ml)					
No HD-induced LVSD	3.34 (2.87- 3.79)	3.49 (2.85-4.05)	3.85 (3.01-4.48)	3.68 (2.97-4.76)	0.7
HD-induced LVSD	3.42 (2.64- 4.35)	3.19 (2.68-4.64)	3.62 (3.14-5.53)	3.78 (3.32-4.78)	
IL-6 (pg/ml)					
No HD-induced LVSD	4.73 (3.00-7.60)	4.32 (2.88-7.75)	4.41 (2.91-7.31)	4.72 (3.21-8.34)	0.8
HD-induced LVSD	7.08 (5.18-8.95)[c]	7.14 (5.15-7.91)	6.84 (4.93-8.11)	6.87 (5.88-9.53)	
IL-10 (pg/ml)					
No HD-induced LVSD	0.39 (0.30-0.57)	0.50 (0.35-0.71)	0.47 (0.34-0.85)	0.46 (0.34-0.82)	0.4
HD-induced LVSD	0.33 (0.23-0.58)	0.37 (0.26-0.84)	0.35 (0.30-0.76)	0.38 (0.25-0.69)	
IL-6/IL-10 ratio					
No HD-induced LVSD	10.7 (6.2-21.1)	8.9 (5.1-15.7)	8.5 (5.3-17.0)	10.1 (5.6-15.8)	0.8
HD-induced LVSD	20.1 (12.4-29.6)[c]	17.5 (9.7-21.7)	15.4 (10.8-23.1)	19.2 (10.3-26.8)	
Bioincompatibility markers					
Leukocytes (10^9/L)					
No HD-induced LVSD	7.08±2.18	6.66±2.03	6.63±1.93	6.47±1.92	0.9
HD-induced LVSD	7.21±2.34	7.06±2.51	7.04±2.27	6.85±2.30	
Neutrophils (10^9/L)					
No HD-induced LVSD	4.33 (3.50-5.51)	4.52 (3.60-5.58)	4.28 (3.39-5.35)	4.03 (3.22-5.29)	0.9
HD-induced LVSD	4.46 (3.52-5.5)	4.71 (3.21-6.04)	4.49 (3.5-5.79)	4.13 (3.21-6.00)	

Myeloperoxidase (ng/ml)					
No HD-induced LVSD	83 (74-101)	192 (158-231)	137 (111-172)	134 (115-169)	0.1
HD-induced LVSD	87 (72-97)	161 (129-212)	133 (95-151)	123 (93-151)	
Complement C3 (g/L)					
No HD-induced LVSD	1.06±0.23	1.11±0.27	1.17±0.32	1.23±0.36	0.2
HD-induced LVSD	1.14±0.25	1.24±0.36	1.29±0.35	1.29±0.32	
Endothelial markers					
sICAM-1 (ng/ml)					
No HD-induced LVSD	142 (123-165)	140 (118-155)	161 (130-200)	180 (152-215)	0.6
HD-induced LVSD	136 (121-156)	131 (114-145)	137 (124-158)	171 (130-206)	
vWF (%)					
No HD-induced LVSD	116.3±42.8	142.0±54.0	133.0±47.3	118.0±43.1	0.1
HD-induced LVSD	133.8±42.9	144.7±70.2	127.1±40.4	126.3±48.0	
Pro-endothelin (pmol/L)					
No HD-induced LVSD	277 (230-316)	245 (198-284)	213 (183-251)	209 (178-241)	0.6
HD-induced LVSD	261 (219-326)	234 (186-300)	217 (168-235)	203 (173-235)	
Endothelin (ng/ml)					
No HD-induced LVSD	41 (25-68)	111 (75-142)	109 (88-194)	97 (74-134)	0.5
HD-induced LVSD	38 (17-61)	103 (47-140)	112 (77-189)	93 (68-159)	

Note: Unless otherwise indicated, values are given as mean ± standard deviation or median (interquartile range).
Abbreviations: HD, hemodialysis; hs-CRP, high sensitivity C-reactive protein; IL, interleukin; LVSD, left ventricular systolic dysfunction; PTX3, pentraxin 3; sICAM-1, soluble intercellular adhesion molecule 1; TNF, tumor necrosis factor; vWF, von Willebrand factor.
[a] P value denotes the comparison between the overall course of biomarkers during HD between patients with and without HD-induced LVSD with correction for baseline concentration.
[b] Denotes the geometrical mean and standard deviation.
[c] Denotes $P<0.05$ for the difference between patients with and without HD-induced regional LVSD; see Results section for the actual P values.

Table 3 Regression Models for the Relationship Between Predialysis Concentration of Markers and Hemodialysis-Induced Regional LV Systolic Dysfunction.

	Univariate		Multivariate[a]	
	OR (95%CI)	P value	OR (95%CI)	P value
Inflammatory markers				
LoghsCRP	2.82(1.10-7.25)	0.03	3.38 (1.02-11.20)	0.05
LogPTX3	6.27 (1.08-36.47)	0.04	2.41 (0.28-21.00)	0.4
LogTNF-α	0.72 (0.05-10.92)	0.8	1.18 (0.05-30.15)	0.9
LogIL-6	3.30 (0.86-12.70)	0.08	2.13 (0.44-10.31)	0.4
LogIL-10	0.34 (0.10-1.16)	0.09	0.21 (0.04-0.97)	0.05
LogIL-6/IL-10 ratio	4.14 (1.42-12.03)	0.009	3.92 (1.20-12.75)	0.02
Bioincompatibility markers				
Leukocytes	1.03 (0.83-1.27)	0.8	1.06 (0.85-1.33)	0.6
Neutrophils	1.03 (0.76-1.41)	0.8	1.05 (0.76-1.46)	0.8
Myeloperoxidase	0.08 (0.003-2.02)	0.1	0.28 (0.01-15.41)	0.5
Complement C3	4.15 (0.65-26.74)	0.1	8.26 (0.85-79.99)	0.07
Endothelial markers				
sICAM	0.53 (0.04-7.56)	0.6	0.44 (0.01-15.0)	0.7
vWF	1.01 (0.99-1.01)	0.08	1.01 (0.99-1.02)	0.4
Pro-endothelin	0.73 (0.01-46.1)	0.9	0.22 (0.001-36.25)	0.6
Endothelin-1	0.33 (0.10-1.11)	0.07	0.28 (0.06-1.27)	0.1

Note: ORs are per 1-unit increase in marker concentration (or logarithm of marker concentration).
Abbreviations: CI, confidence interval; hs-CRP, high sensitivity C-reactive protein; IL, interleukin; LV, left ventricular; OR, odds ratio; PTX3, pentraxin 3; TNF, tumor necrosis factor; sICAM-1, soluble intercellular adhesion molecule 1; vWF, von Willebrand factor.
[a]Corrected for age, sex, dialysis vintage, and predialysis wall motion score index.

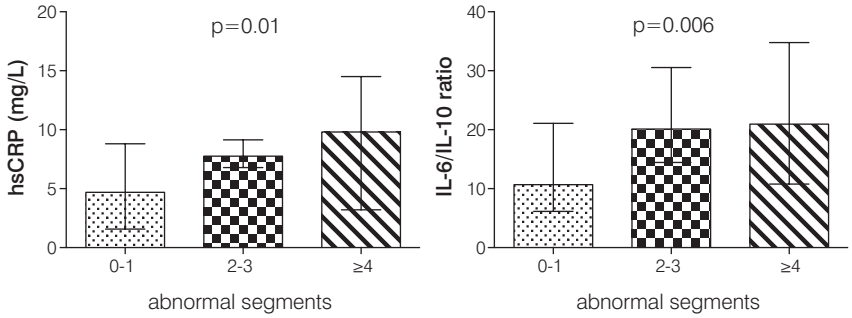

Figure 3 Dose-effect relation between high-sensitivity C-reactive protein (hs-CRP) level and interleukin 6 (IL-6):IL-10 ratio and the number of left ventricular segments that subsequently developed wall motion abnormalities during or after hemodialysis.

P values denote the overall difference.

Discussion

This study shows that patients with hemodialysis-induced regional LV systolic dysfunction have significantly higher predialysis levels of the acute phase proteins hs-CRP and PTX3, higher levels of the proinflammatory cytokine IL-6, and a higher ratio of IL-6 and the anti-inflammatory cytokine IL-10. The intradialysis course of markers of bioincompatibility (leukocytes, neutrophils, myeloperoxidase, and C3) and the rapid-response PTX3 did not differ between patients with and without hemodialysis-induced regional LV systolic dysfunction. Therefore, the more pronounced systemic inflammation in patients with hemodialysis-induced regional LV systolic dysfunction does not seem to originate from an exaggerated bioincompatibility reaction to hemodialysis.

Levels of most circulating acute-phase proteins and proinflammatory cytokines are elevated in hemodialysis patients compared with apparently healthy controls[17] and higher levels are associated with increased risk of mortality and cardiovascular events[7,18-21].The association between inflammation and hemodialysis-induced cardiac dysfunction has not been reported before. In the present study, predialysis levels of hs-CRP, PTX3, IL-6, and the IL-6:IL-10 ratio were all significantly higher in patients who subsequently developed hemodialysis-induced regional LV systolic dysfunction. In multivariate analyses, IL-6 level lost its significant association, but higher hs-CRP level, higher IL-6:IL-10 ratio, and lower IL-10 level remained as independent factors associated with the development of cardiac dysfunction during hemodialysis. Interestingly, hs-CRP and IL-6:IL-10 ratio values showed a dose-response relation,

with higher levels in patients who developed a greater number of regional wall motion abnormalities during hemodialysis. These results strongly suggest that there is a link between systemic inflammation and the development of hemodialysis-induced regional LV systolic dysfunction. Inflammation could have a pathophysiologic function in the development of LV systolic dysfunction during hemodialysis, for example, by increasing the susceptibility for cardiac ischemia through a negative effect of inflammation on endothelial function of the myocardial microcirculation[22] and/or by cardiodepressive effects of proinflammatory cytokines and complement factors[9,23,24]. However, at present, these mechanisms are speculative. There are several other theoretical possibilities for the link between hemodialysis-induced regional LV systolic dysfunction and inflammation. First, the higher inflammatory marker levels may reflect a higher atherosclerotic burden[6,19]. Second, other causes of inflammation may be involved, such as periodontal disease or dialysis access–related infections. Recently, McIntyre et al[25] showed that patients with hemodialysis-induced cardiac dysfunction had higher endotoxin levels than patients in whom LV function was not affected by hemodialysis. Third, higher levels of inflammation markers may be a consequence rather than a cause of hemodialysis-induced cardiac dysfunction. Myocardial ischemia-reperfusion induces an inflammatory response[26,27] and thus repetitive myocardial ischemia-reperfusion elicited by hemodialysis may result in chronic elevation of inflammatory marker levels. This may initiate a vicious cycle in which elevated proinflammatory cytokine concentrations further impair cardiac function. However, this mechanism cannot be confirmed in the existing data and is speculative.

There are scarce data for the course of inflammatory marker levels during hemodialysis. Several studies have shown that inflammatory marker levels are higher postdialysis compared with predialysis[28,29]. Previous reports of the intradialysis course of CRP levels did not yield uniform results, with some studies reporting no change[15,29] whereas Korevaar et al[30] observed an increase in CRP levels in 25% of patients. In the present study, CRP levels did not change significantly during hemodialysis. In contrast, in line with a recent study,[15] PTX3 levels increased significantly during hemodialysis; however, there was no difference between patients with and without hemodialysis-induced regional LV systolic dysfunction. Although IL-6 level is known to increase slower than PTX3 level, peaking 2-6 hours after an activating stimulus, Yamamoto et al[15] observed a significant increase in IL-6 levels during hemodialysis. In contrast, we did not observe an increase in IL-6 levels during dialysis. This may be related to the use of a more biocompatible membrane in our study (polysulfone). In line with previous studies, we found a small but significant decrease in leukocyte and neutrophil counts during hemodialysis[31]. This has been attributed to activation in the extracorporal system and subsequent sequestration in (mainly) the pulmonary vasculature. Leukocyte activation during hemodialysis also is evidenced by increases in plasma myeloperoxidase levels due to leukocyte

degranulation. In line with earlier reports, we observed a significant increase in myeloperoxidase levels early during dialysis[31]. Similarly, C3 levels increased significantly during dialysis, consistent with previous studies[32,33]. Notably, patients with hemodialysis-induced regional LV systolic dysfunction did not have greater decreases in leukocyte and neutrophil counts or greater increases in myeloperoxidase and C3 levels during dialysis, arguing against a greater bioincompatibility reaction in these patients. This study has several limitations. First, we did not perform coronary angiography or computed tomography for quantification of coronary calcifications in our patients and therefore could not relate markers of inflammation to extent of atherosclerosis. Second, we did not measure circulating endotoxin as a possible source of systemic inflammation. Finally, our study population is relatively small, especially the group with hemodialysis-induced regional LV systolic dysfunction.

Our study has several strengths. Despite the relatively small sample size, to our knowledge, this is the largest study to date on the acute effect of hemodialysis on cardiac function in relation to markers of inflammation, bioincompatibility, and endothelial function. These markers were measured not only before but also at several times during hemodialysis and were corrected for hemoconcentration.

In conclusion, patients with hemodialysis-induced regional LV systolic dysfunction have significantly higher predialysis levels of various inflammatory markers. The source of the systemic inflammation is unknown, but it does not seem to originate from an exaggerated bioincompatibility reaction to hemodialysis because the intradialysis courses of levels of inflammation and bioincompatibility markers did not differ between participants with and without hemodialysis-induced regional LV systolic dysfunction.

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Supplementary material

Table S1: Association between predialysis regional and global systolic function and inflammatory, bioincompatibility, and endothelial markers.

Table S2: Most predictive combination of inflammatory markers for occurrence of HD-induced regional LV systolic dysfunction.

Table S3: Predialysis, intradialysis, and postdialysis biomarker concentrations in all patients.

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Supplementary Table 1 The association between predialysis regional (WMSI) and global (LVEF) systolic function and inflammatory, bioincompatibility, and endothelial markers.

	Predialysis WMSI			Predialysis LVEF		
	Normal (WMSI=1) N= 63	Abnormal (WMSI>1) N= 42	P value	Normal (EF≥50%) N= 72	Abnormal (EF<50%) N = 33	P value
Inflammatory markers						
hsCRP	4.3 (1.7-8.8)	8.1 (4.7-12.8)	0.02	4.7 (1.7-8.9)	7.7 (4.7-14.2)	0.09
PTX3	2.5 (1.6-3.7)	3.0 (1.6-4.3)	0.24	2.4 (1.6-3.7)	3.0 (2.2-4.9)	0.02
TNF-α	3.3 (2.9-3.8)	3.5 (2.7-4.2)	0.59	3.3 (2.8-3.9)	3.4 (2.9-4.0)	0.49
IL-6	4.8 (3.5-7.6)	7.1 (4.1-9.0)	0.06	4.8 (3.0-7.1)	8.3 (5.3-13.8)	<0.001
IL-10	0.38 (0.27-0.54)	0.40 (0.27-0.58)	0.97	0.36 (0.25-0.51)	0.49 (0.32-0.64)	0.04
IL-6/IL-10 ratio	11.0 (7.2-22.0)	16.5 (10.1-29.6)	0.11	12.1 (6.9-24.0)	15.3 (9.5-29.6)	0.26
Bioincompatibility markers						
Leukocytes	7.0 ± 2.0	7.3 ±2.5	0.58	7.2 ±2.3	6.9 ± 2.1	0.60
Neutrophils	4.3 (3.6-5.5)	4.5 (3.5-5.5)	0.68	4.3 (3.7-5.5)	4.2 (3.2-5.7)	0.57
Myeloperoxidase	89.0 (74.5-103.9)	83.7 (71.8-93.0)	0.25	88.5 (73.9-105.9)	82.6 (70.8-92.5)	0.13
Complement C3	1.07 ± 0.25	1.11 ± 0.22	0.31	1.09 ± 0.23	1.08 ± 0.25	0.89
Endothelial markers						
sICAM	138 (121-158)	144 (128-162)	0.38	138 (121-158)	142 (125-163)	0.48
vWF	116.2 ± 45.3	128.0 ± 39.8	0.18	118.2 ± 43.0	127.3 ± 44.0	0.34
Pro-endothelin	268 (225-310)	273 (235-333)	0.33	275 (222-311)	268 (236-340)	0.35
Endothelin-1	41 (26-72)	35 (17-57)	0.14	41 (21-68)	36 (25-63)	0.74

Abbreviations: WMSI, wall motion score index; LVEF, Left ventricle ejection fraction; N: number; hsCRP, high sensitivity C-reactive protein; PTX3, pentraxin 3; TNF, Tumor Necrosis Factor; IL-6, interleukin 6; IL-10, interleukin 10; sICAM-1, Soluble Intercellular Adhesion Molecule 1; vWF, von Willebrand Factor.

Supplementary Table 2 The most predictive combination of inflammatory markers for the occurrence of hemodialysis-induced regional LV systolic dysfunction.

	HR	CI	P value
loghsCRP¶	4.36	1.17-16.2	0.028
logIL-10§	0.16	0.03-0.87	0.034

¶ corrected for age, gender, dialysis vintage, predialysis WMSI and logIL-10.
§ corrected for age, gender, dialysis vintage, predialysis WMSI and loghsCRP.

Chapter 7

Prognostic Aspects of Hemodialysis-induced Regional Left Ventricular Systolic Dysfunction

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Submitted

Abstract

Background and objectives: Hemodialysis may acutely induce regional left ventricular (LV) systolic dysfunction (stunning). Here, we studied the evolution of LV systolic function and the prognostic value of hemodialysis-induced regional LV systolic dysfunction.
Design, setting, participants, and measurements: Hundred-five patients on a thrice-weekly hemodialysis schedule were studied between March 2009 and March 2010. Echocardiography was performed at predialysis, 60 and 180 min intradialysis and 30 min postdialysis. Hemodialysis-induced regional LV dysfunction was defined as an increase in wall motion score (WMS) in ≥2 segments compared with predialysis. Patients were followed for 2 years for the occurrence of mortality and cardiac events. After one year, global (LV ejection fraction, LVEF) and regional (WMS index, WMSI) systolic function was again evaluated by predialysis echocardiography.
Results: Hemodialysis-induced regional LV systolic dysfunction occurred in 29 (28%) patients. These patients had a higher incidence of all-cause mortality (HR: 3.80, CI: 1.26-11.41, p=0.02) and cardiac events (HR: 3.77, CI: 1.05-13.63, p=0.04) after adjustment for age, gender, dialysis vintage, cardiovascular history, diabetes, ultrafiltration volume, LVMI, and predialysis WMSI at baseline. The evolution of global systolic function did not differ between groups, whereas a non-significantly greater proportion of patients with hemodialysis-induced regional LV systolic dysfunction had an increase in the number of LV regions with abnormal WMS after one year (50% versus 23%, p=0.07).
Conclusions: Hemodialysis-induced regional LV systolic dysfunction was independently associated with all-cause mortality and cardiac events. This entity was not associated with global change in systolic dysfunction after one-year, but tended to be associated with progression of regional LV dysfunction.

Introduction

Hemodialysis patients have high cardiac morbidity and mortality rates[1,2]. It is increasingly recognized that the hemodialysis procedure itself may acutely induce cardiac dysfunction[3-6]. With the use of positron emission tomography scanning during hemodialysis, we and others showed that a regular hemodialysis session is associated with a significant reduction in myocardial blood flow[7,8]. In some patients the fall in myocardial blood flow resulted in reversible LV systolic dysfunction, especially in regions with the greatest fall in myocardial blood flow[7,8], suggestive of ischemia-induced cardiac stunning. Repetitive hemodialysis-induced regional myocardial ischemia of sufficient intensity to result in regional LV dysfunction may lead to cumulative LV dysfunction and contribute to the progression of heart failure, cardiac arrhythmias, and increased mortality[9,10]. Two recent studies have indeed shown that patients who develop regional wall motion abnormalities during hemodialysis have a higher incidence of all-cause mortality[11,12] and one of these studies also reported a higher incidence of the combined outcome of mortality and cardiovascular events[11]. Burton et al also found an association between hemodialysis-induced regional LV systolic dysfunction and subsequent deterioration of global and regional LV function[11,13]. The echocardiographic technique to assess hemodialysis-induced regional LV systolic dysfunction in these studies is not routinely used in clinical patient care. In the present study, we assessed global and regional systolic LV dysfunction according to clinically easily applicable methods as recommended by the European Society of Echocardiography[14]. Our major aim was to investigate the prognostic impact of hemodialysis-induced regional LV systolic dysfunction, assessed with this technique, on all-cause mortality and cardiac events with adjustment for possible confounders. Our second aim was to evaluate whether the occurrence of hemodialysis-induced regional LV systolic dysfunction is associated with a change in global and/or regional LV systolic function over 1 year.

Materials and Methods

Patients and study design

Hemodialysis patients from the Dialysis Center Groningen and the University Medical Center Groningen were eligible for this study if they were treated with hemodialysis for more than 3 months and were on a thrice-weekly hemodialysis schedule. Patients with severe heart failure (NYHA stage IV) and patients that did not have an adequate window for echocardiography imaging were excluded.

Patients were studied at the dialysis session following the longest interdialytic interval (3 days). The dialysis duration was 4 hours. Patients' characteristics were

assessed at entry into the study (Table 1). Diabetes was defined as fasting blood glucose >6 mmol/l or the use of anti-diabetic drugs. Hypertension was defined as a predialysis systolic blood pressure >140 and/or diastolic blood pressure >90 mmHg, or the use of antihypertensive drugs. Cardiovascular history was defined as any history of ischemic heart disease, congestive heart failure, Coronary Artery Bypass Grafting, Percutaneous Coronary Intervention, stroke, or peripheral vascular disease. These data were collected from hospital medical charts.

Ultrafiltration rate was expressed in ml/kg/h by dividing the ultrafiltration volume by target weight and dialysis session length[15]. Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentration according to the second-generation logarithmic Daurgirdas equation[16]. The study was performed according to the Declaration of Helsinki and was approved by the Medical Ethical Committee of the University Medical Center Groningen. All patients gave written informed consent. The baseline echocardiography study was performed between March 2009 and March 2010.

Dialysis settings

All patients were on bicarbonate dialysis with a low-flux polysulfone hollow-fiber dialyser (F8, Fresenius Medical Care, Bad Hamburg, Germany). Blood flow and dialysate flow rates were 250-350 and 500 ml/min, respectively. Dialysate temperature was 36.0 °C in all patients. Dialysate composition was sodium 139 mmol/l, potassium 1.0 or 2.0 mmol/l, calcium 1.5 mmol/l, magnesium 0.5 mmol/l, chloride 108 mmol/l, bicarbonate 34 mmol/l, acetate 3.0 mmol/l, and glucose 1.0 g/l. We used constant ultrafiltration rate and dialysate conductivity. The water for hemodialysis complied with the requirements of the European Pharmacopoeia (<100 colony forming units/mL; <0.25 endotoxin units/mL). Patients received a light meal after the echocardiography at 60 min intradialysis. All patients were dialysed in supine position, which was convenient for echocardiography and excluded the effect of posture changes on blood volume.

Echocardiography examination

A dedicated team of three experienced technicians performed two-dimensional echocardiography using a General Electric VIVID 7 system with a 2.5-mHz probe. At baseline, echocardiography was performed four times: before hemodialysis, at 60 and 180 min after the start of hemodialysis, and 30 min after the end of hemodialysis. One experienced technician (YMH) performed all the analyses off-line according to the guidelines of European Society of Echocardiography[14]. At least three consecutive heartbeats in each view were acquired. Global and regional systolic function was evaluated by LV ejection fraction (LVEF) and wall motion score index (WMSI), respectively. LVEF was assessed using the eye-balling method. WMSI was evaluated

according to the 16-segments model as recommended by the European Society of Echocardiography[14] by a single technician (YMH) who was blinded to the order of echocardiography studies. For each patient, the number of LV regions (from a total of 16) that developed new (not present before hemodialysis) regional wall motion abnormalities (RWMA) during/after hemodialysis was calculated. RWMA during/after hemodialysis was defined as an increase in wall motion score in that specific LV segment occurring at either 60 min intradialysis, 180 min intradialysis, or 30 min postdialysis in comparison with predialysis. Hemodialysis-induced regional LV systolic dysfunction was defined as the development of new RWMA during/after hemodialysis in two or more LV segments compared with predialysis. LV mass index (LVMI) was calculated as described previously[17].

Follow-up

The primary outcome parameter was the incidence of all-cause mortality during a follow-up period of 2 years. Secondary outcomes were cardiac events and the combined incidence of all-cause mortality and cardiac events during the follow-up period of 2 years. Cardiac events were defined as occurrence of ischemic heart disease (unstable angina pectoris, myocardial infarction, Coronary Artery Bypass Grafting and/or Percutaneous Coronary Intervention), sudden cardiac death, and congestive heart failure. Combined outcome was the occurrence of first fatal or non-fatal cardiac event or mortality of any cause. Transplantation was a censoring event and the transplantation date was considered as the final follow-up date. Data endpoints regarding survival and cardiac events were obtained from hospital charts.

The change in global and regional LV function during a period of one year was assessed by comparing the predialysis echocardiography parameters from the baseline study with similar parameters that were obtained with a predialysis echocardiography one year later. The methods for evaluation of LVEF, WMSI, and LVMI were similar as for the baseline echocardiography.

Laboratory procedures

Blood samples were collected from the arterial line of dialysis circuit at the start of hemodialysis. Hematocrit, plasma albumin, total calcium, magnesium, and phosphate levels were immediately determined. For the determination of cytokines, blood was centrifuged within 30 min of collection at 3500 rpm for 15 min. Supernatants were stored at -80 °C until measurement. Prior to assay, samples were thawed and re-centrifuged. Samples were analyzed at a single time point to eliminate inter-assay variability. Laboratory personnel were unaware of patient data or outcome.

High-sensitive CRP (hsCRP) was measured with N latex CRP monoassay (Siemens Diagnostic, Newark, DE, USA). Pentraxin 3 (PTX3), Interleukin-6 (IL-6), and interleukin-10 (IL-10) were measured by quantitative sandwich enzyme immunoassay

technique (R&D system, Minneapolis, MN, USA). TNF-α was measured by Quantikine HS Human immunoassay (R&D system, Minneapolis, MN, USA).

Statistical analysis

Data are reported as mean $\pm$ SD for continuous variables with normal distributions, median (interquartile range) for skewed variables, and number (%) for categorical data. Comparisons with baseline were made by paired t-test and sign-ranked test for variables with normal distributions and skewed variables, respectively. Survival curves for all-cause mortality, cardiac events and the combined outcome were computed by Kaplan-Meier method. Multivariate Cox proportional hazards model was used to evaluate the association between hemodialysis-induced regional LV systolic dysfunction and all-cause mortality, cardiac events, and the combined outcome. Model 1 was the crude model. Model 2 was adjusted for age and gender. Model 3 was adjusted for age and gender and, additionally, for dialysis vintage, diabetes, cardiovascular history, ultrafiltration volume, LVMI, and predialysis WMSI at baseline. The change in systolic function and LVMI after one-year follow up was compared with baseline using Wilcoxon sign-ranked and Student t-test, respectively. Generalized estimation equation models were used to assess the difference in the courses of systolic function and LVMI between the two groups. The difference in the number of patients that had a change in the number of RWMA at the predialysis echocardiography during one year between patients with and without hemodialysis-induced regional LV systolic dysfunction was evaluated using X^2 test. Two-sided P value <0.05 was considered as significant. Statistical analyses were performed with STATA version 11 (StataCorp LP, College Station, TX, USA) and SPSS version 20 (SPSS Inc. Chicago, IL, USA).

Results

Patient characteristics

The recruitment process of participants is outlined in Figure 1. One hundred and nine patients participated in this study. Four patients were excluded from the analysis since it was not possible to reliably assess the per-segment LV function during hemodialysis.

At baseline, twenty-nine patients (28%) developed new RWMA in two or more LV segments at either 60 min intradialysis, 180 min intradialysis, or 30 min postdialysis and, thus, fulfilled the definition of hemodialysis-induced regional LV systolic dysfunction. The characteristics of the total patient group and the subgroup of patients with follow-up echocardiography after one year are outlined in Table 1. In the total group of 105 patients, there were no significant differences in baseline

characteristics between patients with and without hemodialysis-induced LV dysfunction except gender, and predialysis WMSI: patients with hemodialysis-induced regional LV systolic dysfunction were more frequently of male gender ($p=0.05$) and had a higher predialysis WMSI ($p<0.001$), indicating worse predialysis regional LV systolic function (Table 1).

Sixty-three patients underwent follow-up echocardiography after one year. Ten of these patients had hemodialysis-induced regional LV systolic dysfunction at the baseline study. Baseline patient characteristics of the 63 patients with follow-up

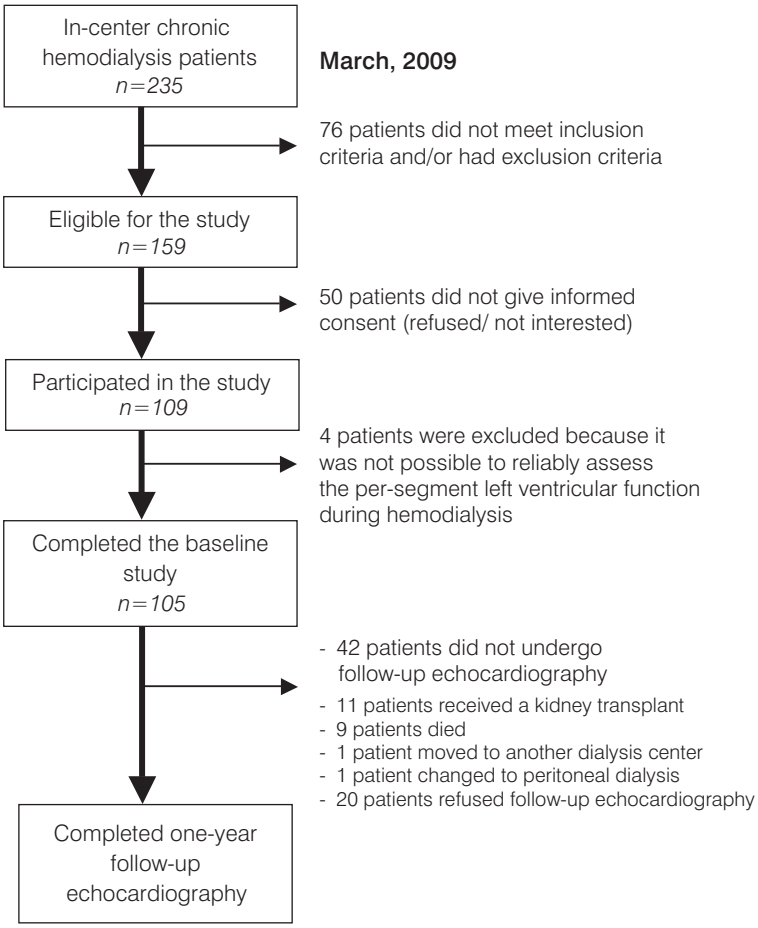

Figure 1 Recruitment process of study participants.

Table 1 Patient characteristics at baseline.

	All patients (n=105)			Patient with one-year follow-up echocardiography (n=63)		
	HD-induced regional LV dysfunction			HD-induced regional LV dysfunction		
	Yes (n=29)	No (n=76)	P value	Yes (n=10)	No (n=53)	P value
Age (y)	69 (58-78)	64 (50-75)	0.1	70 (58-78)	65 (51-75)	0.2
Male gender (%)	23 (79)	45 (59)	0.05	8 (80)	29 (55)	0.1
Dialysis vintage (mo)	18.4 (5.5-49.7)	24.0 (8.3-48.3)	0.7	27.5 (6.9-59.5)	24.4 (10.6-50.5)	0.9
Diabetes (%)	4 (14)	19 (25)	0.3	1 (10)	16 (30)	0.2
Hypertension (%)	23 (79)	61 (80)	0.9	8 (80)	42 (79)	0.8
Cardiovascular history (%)	8 (28)	15 (20)	0.3	2 (20)	13 (25)	0.8
BMI (kg/m^2)	25.2 (23.2-27.8)	25.2 (22.6-28.3)	0.9	24.4 (23.4-25.3)	25.2 (22.6-28.1)	0.7
Primary renal disease (%)						
Hypertension	5 (17.2)	12 (15.8)	0.9	1 (10.0)	11 (20.8)	0.4
Diabetes	2 (6.9)	11 (14.5)	0.3	0 (0)	9 (17.0)	0.2
ADPKD	4 (13.8)	10 (13.2)	0.9	3 (30.0)	6 (11.3)	0.1
FSGS	2 (6.9)	8 (10.5)	0.6	1 (10.0)	5 (9.4)	0.9
IgA nephropathy	0 (0)	4 (5.3)	0.2	0 (0)	3 (5.7)	0.4
Chronic pyelonephritis	0 (0)	1 (1.3)	0.5	0 (0)	1 (1.9)	0.7
Glomerulonephritis	3 (10.3)	10 (13.2)	0.7	1 (10.0)	7 (13.2)	0.8
Other diagnoses	6 (20.6)	10 (13.2)	0.3	2 (20.0)	4 (7.6)	0.2
Unknown	7 (24.1)	10 (13.2)	0.2	2 (20.0)	7 (13.2)	0.6
Medication (%)						
Aspirin	11 (37.9)	46 (60.5)	0.08	7 (70.0)	32 (60.4)	0.6
CCB	2 (6.9)	12 (15.8)	0.3	2 (20.0)	9 (17.0)	0.8
β-Blocker	15 (51.7)	45 (59.2)	0.5	6 (60.0)	29 (54.7)	0.8

ACE inhibitor	2 (6.9)	8 (10.5)	0.6	2 (20.0)	5 (9.4)	0.3
ARB	4 (13.8)	10 (13.2)	0.8	2 (20.0)	7 (13.2)	0.6
Statin	6 (20.7)	14 (18.4)	0.7	3 (30.0)	9 (17.0)	0.3
Hematocrit	34.6±2.9	35.1±4.0	0.6	35.8±2.6	34.9±3.9	0.5
Albumin (g/l)	39 (37-41)	39 (37-42)	0.7	40 (37-41)	39 (38-42)	0.9
Calcium (mmol/l)	2.33±0.14	2.33±0.17	0.9	2.33±0.11	2.33±0.15	0.9
Phosphate (mmol/l)	1.7±0.5	1.7±0.6	0.9	1.8±0.6	1.6±0.5	0.3
Magnesium (mmol/l)	1.03±0.17	1.08±0.18	0.2	1.00±0.12	1.09±0.17	0.1
Kt/V	4.18±0.66	4.35±0.73	0.3	4.11±0.75	4.46±0.74	0.2
Ultrafiltration volume (L)	2.58±0.93	2.54±0.74	0.8	2.78±0.71	2.52±0.73	0.3
Ultrafiltration rate (ml/kg/h)	8.32±2.97	8.63±2.52	0.6	8.82±1.60	8.65±2.63	0.8
Predialysis WMSI	1.23 (1.06-1.48)	1.00 (1.00-1.03)	<0.001	1.13 (1.06-1.44)	1.00 (1.00-1.00)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous Abbreviations: HD: hemodialysis; LV: left ventricular; SD: standard deviation; n: number; IQR: interquartile range, BMI: body mass index; ADPKD: Adult dominant polycystic kidney disease; FSGS: focal segmental glomerulosclerosis; CCB: calcium channel blocker; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; WMSI: wall motion score index.

echocardiography were comparable with the baseline characteristics of the total group of 105 patients, both for patients with and without hemodialysis-induced regional LV systolic dysfunction (table 1).

Table 2 Causes of mortality and type of cardiac event during a follow-up period of 2 years.

	HD-induced regional systolic LV dysfunction (n=29)	No HD-induced regional systolic LV dysfunction (n=76)	P value
Mortality			
Mortality of any cause	10 (35%)	10 (15%)	0.01
Cardiac	5 (17%)	5 (7%)	0.09
Infection	0 (0%)	1 (1%)	0.54
Stop dialysis treatment	2 (7%)	4 (5%)	0.75
Other	2 (7%)	0 (0%)	0.02
Unknown	1 (4%)	0 (0%)	0.10
Cardiac events			
Any cardiac event	8 (28%)	12 (16%)	0.17
Ischemic heart disease	6 (21%)	7 (9%)	0.11
Sudden cardiac death	1 (4%)	3 (4%)	0.91
Heart failure	1 (4%)	2 (3%)	0.82
Combined outcome of mortality and cardiac events	13 (45%)	18 (24%)	0.03

Abbreviations: HD: hemodialysis; LV: left ventricular; n=number.

All-cause mortality, cardiac events, and combined outcome during follow-up

During 2 years of follow-up, 20 patients (19%) died, 20 patients (19%) developed cardiac events, and 31 patients (30%) had the combined outcome. Causes of death and specific cardiac events are reported in table 2. All-cause mortality was significantly higher among patients with hemodialysis-induced regional LV systolic dysfunction (p=0.01). Mortality due to a cardiac cause tended to be higher in patients with hemodialysis-induced regional LV systolic dysfunction (p=0.09). The incidence of cardiac events was higher in patients with hemodialysis-induced regional LV systolic dysfunction but the difference was not statistically significant (p=0.17). The difference in cardiac event rates between the groups was mainly due to a higher incidence of ischemic

heart disease in patients with hemodialysis-induced regional LV dysfunction but the difference with patients with preserved LV systolic function during hemodialysis was not statistically significant (p=0.11). The combined outcome of all-cause mortality and cardiac events was significantly higher in patients with than in those without hemodialysis-induced regional LV systolic dysfunction (p=0.03). The Kaplan-Meier graphs for all-cause mortality, cardiac events, and the combined outcome are depicted in Figure 2.

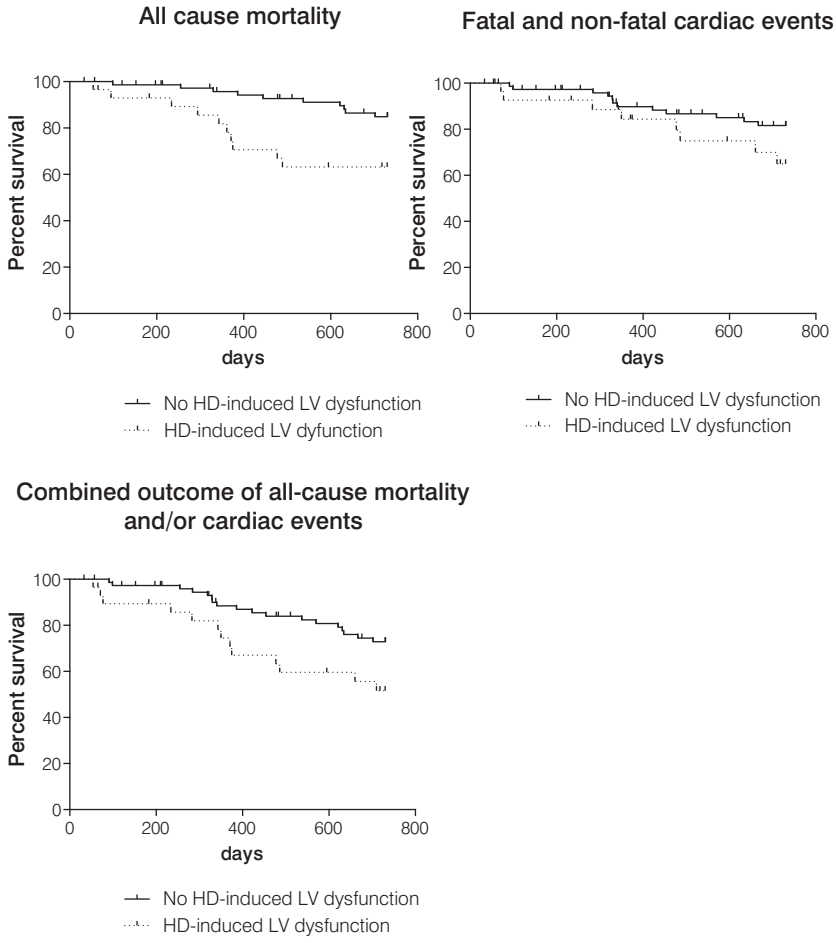

Figure 2 Kaplan-Meier graphs for all-cause mortality (upper left panel), fatal and non-fatal cardiac events (upper right panel), and combined outcome (lower panel) during 2-years of follow-up.

In the Cox regression models, patients with hemodialysis-induced regional LV systolic dysfunction had significantly higher all-cause mortality after adjustment for age, gender, dialysis vintage, cardiovascular history, diabetes, ultrafiltration volume, LVMI, and predialysis WMSI at baseline (HR: 3.80; CI: 1.26-11.41; p=0.02) (table 3). Likewise, the incidence of cardiac events was significantly higher in patient with hemodialysis-induced regional LV systolic dysfunction (HR: 3.77; CI:1.05-13.63; p=0.04), after adjustment for the same factors. The combined outcome of mortality and cardiac events was significantly higher in patients with hemodialysis-induced regional LV dysfunction after adjustment for the factors mentioned above (p=0.02). Additional adjustment of the prognostic effect of hemodialysis-induced regional LV systolic dysfunction for various inflammatory markers (CRP, pentraxin 3, Il-6, TNF alpha, Il-6 and the Il-6:Il-10 ratio), did not substantially change the associations between hemo-

Table 3 Prognostic effects of hemodialysis-induced regional LV dysfunction on all-cause mortality, cardiac events, and the combined outcome of mortality and cardiac events during a follow-up period of 2 years.

	HR	CI	P value
All-cause Mortality			
Model 1: crude model	3.09	1.29-7.43	0.01
Model 2: age and gender	2.52	1.03-6.15	0.04
Model 2: age, gender, dialysis vintage, cardiovascular history, diabetes, ultrafiltration volume, LVMI, and predialysis WMSI	3.80	1.26-11.41	0.02
Cardiac events			
Model 1: crude model	2.01	0.82-4.93	0.13
Model 2: age and gender	1.91	0.76-4.77	0.17
Model 2: age, gender, dialysis vintage, cardiovascular history, diabetes, ultrafiltration volume, LVMI, and predialysis WMSI	3.77	1.05-13.63	0.04
Combined outcome of mortality and cardiac event			
Model 1: crude model	2.19	1.07-4.47	0.03
Model 2: age and gender	1.89	0.91-3.91	0.09
Model 2: age, gender, dialysis vintage, cardiovascular history, diabetes, ultrafiltration volume, LVMI, and predialysis WMSI	3.02	1.23-7.43	0.02

Abbreviations: HR: Hazard ratio; CI: Confidence interval; LV: left ventricular; LVMI: left ventricular mass index; WMSI: wall motion score index

dialysis-induced regional LV systolic dysfunction and all-cause mortality, cardiac events, and the combined outcome, with comparable hazard ratios after adding each of the (anti-)inflammatory markers (supplementary table 1).

Evolution of LV systolic function during one year of follow-up

The evolution of LV systolic parameters is shown in Figure 3. LVEF did not change significantly during the one-year follow-up in the whole group (p=0.98) nor in the

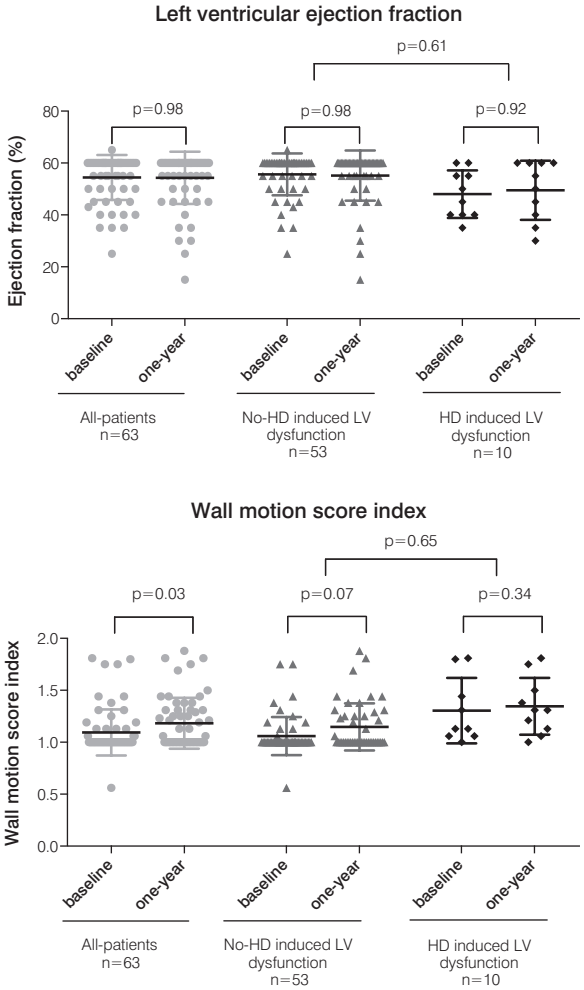

Figure 3 Echocardiographic parameters at baseline and after one year in the subgroup of patients that had follow-up echocardiography after one year.

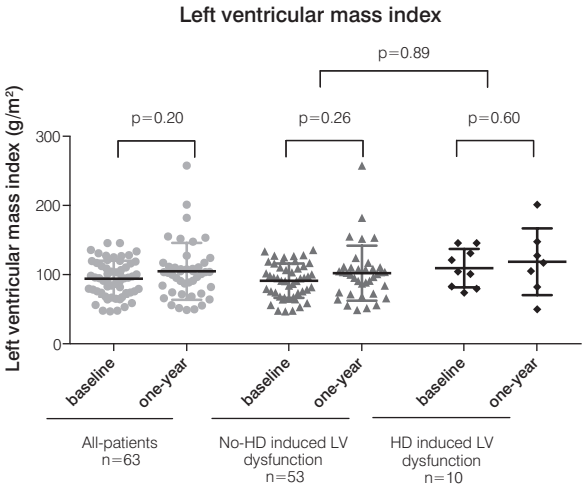

Figure 3 Continued.

subgroups of patients with (p=0.92) and those without (p=0.98) hemodialysis-induced regional LV systolic dysfunction at baseline. In the total patient group, WMSI rose significantly during the one year of follow-up compared with baseline (p=0.03). However, WMSI did not change significantly in the subgroups of patients with and without hemodialysis-induced regional LV systolic dysfunction, although it tended to increase significantly in the latter group (p=0.07). LVMI did not change significantly during the one-year follow-up in neither the total patient group nor in the subgroups of patients with and without hemodialysis-induced regional LV systolic dysfunction (p=0.20, p=0.60, and p=0.26, respectively). The overall course of the change in LVEF, WMSI and LVMI did not significantly differ between patients with and without hemodialysis-induced regional LV systolic dysfunction (p=0.61, p=0.65 and p=0.89, respectively).

In the subgroup of 10 patients with hemodialysis-induced regional LV systolic dysfunction during the baseline study, 5 patients (50%) had an increase and 5 patients (50%) had no change or a decrease in the number of RWMA at the predialysis echocardiography during the one-year follow-up. In the subgroup of 53 patients without hemodialysis-induced regional LV systolic dysfunction during the baseline study, 12 patients (23%) had an increase and 41 patients (77%) had no change or a decrease in the number of predialysis RWMA during one-year of follow-up. The difference between the two groups tended to be significant (p=0.07) (Figure 4).

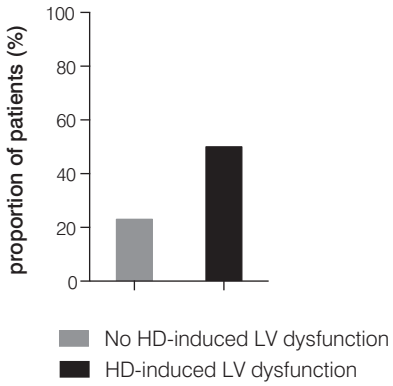

Figure 4 Proportion of patients with an increased in the number of predialysis RWMA during the one-year interval between the baseline study and follow-up echocardiography according to the presence or absence of hemodialysis-induced regional LV systolic dysfunction at the baseline study.

Discussion

In this study we found that the occurrence of hemodialysis-induced regional LV systolic dysfunction was independently associated with a higher incidence of all-cause mortality and cardiac events. The dominant type of cardiac events was ischemic heart disease. The evolution of global LV systolic function did not differ significantly between patients with and those without hemodialysis-induced regional LV systolic dysfunction, although the former group tended to have an increase in the number of LV regions with RWMA after one year.

Recent studies have shown that regional LV systolic dysfunction/ myocardial stunning occurs relatively frequent during hemodialysis and is associated with a higher incidence of all-cause mortality during a follow period of 1 year and 1.5 year, respectively [11,12]. In the study of Burton et al, the occurrence of hemodialysis-induced myocardial stunning was also associated with a higher incidence of the composite outcome of cardiovascular events and mortality[11]. In this study, with a follow-up period of two years, we confirm that patients with hemodialysis-induced regional LV systolic dysfunction have a higher incidence of all-cause mortality, also after correction for age, gender, dialysis vintage, diabetes, cardiovascular events, ultrafiltration volume, LVMI, and predialysis WMSI at baseline. Hemodialysis-induced regional LV systolic dysfunction also appeared to be an independent risk factor for the occurrence of cardiac events.

Cardiac causes were the most prevalent cause of mortality in our patient group, a result consistent with prior reports[11]. The dominant type of cardiac events was ischemic heart disease but we found no significant difference in the incidence of ischemic heart disease between patients with and without hemodialysis-induced regional LV systolic dysfunction. The incidence of sudden cardiac death was low compared with previous studies[5, 18-20] and did also not differ between patients with and without hemodialysis-induced regional LV systolic dysfunction. A previous study has shown that patients with hemodialysis-induced regional LV systolic dysfunction have a higher incidence of arrhythmias[21]. Although this study has limited power to detect differences in specific cardiac outcomes, our findings suggest that the risk of sudden cardiac death is not increased in patients with hemodialysis-induced regional LV systolic dysfunction.

We previously found a significant association between hemodialysis-induced regional LV dysfunction and higher predialysis levels of the inflammatory markers CRP, pentraxin 3, and Il-6 and lower levels of the anti-inflammatory marker Il-10[22]. In the present study we, therefore, analyzed whether adding these markers to the model modified the prognostic effect of hemodialysis-induced regional LV dysfunction. It appeared that the association between hemodialysis-induced regional LV dysfunction and outcome was independent of the predialysis levels of these (anti-) inflammatory markers.

Studies with serial echocardiographic evaluation in hemodialysis patients have shown that deterioration in systolic LV function as well as an increase in LVMI over one year is associated with a higher incidence of cardiac failure and that regression of LV systolic dysfunction is associated with a better cardiac outcome[23-25]. It can be expected that patients who develop regional LV systolic dysfunction during hemodialysis, also experience a faster deterioration of global and/or regional LV systolic function over time. Burton et al reported a significantly faster deterioration of LVEF during one year in the subgroup of patients with hemodialysis-induced RWMA[11]. We found that LV systolic function measured by LVEF remained unchanged during one-year of follow up, both in the total patient population and in the subgroups with and without hemodialysis-induced regional LV systolic dysfunction. This is consistent with an earlier study that showed that LVEF did not change prominently in hemodialysis patients during one-year of follow-up[25]. At the same time, we found that WMSI increased significantly during one year in the total study population indicating progression of regional LV systolic dysfunction. However, we did not observe a significant difference in the course of WMSI between patients with and without hemodialysis-induced regional LV systolic dysfunction. Notably, we should be cautious with conclusions on subgroups because of the relatively small number of patients that had follow-up echocardiography, especially the patient group with hemodialysis-induced regional LV dysfunction. Burton et al found that 90% of patients with RWMA occurring during hemodialysis continue to have these regional LV abnormalities during dialysis one year later. Almost half of these patients showed a progression of

the number of affected LV regions during this year[11]. We did not study the development of per-segment RWMA during hemodialysis after one year of follow-up but with predialysis echocardiography we found that the percentage of patients with an increase in the number of affected segments during one year was higher among patients with compared with those without hemodialysis-induced regional LV systolic dysfunction at baseline (50% vs. 23%) but the difference was not significant ($p=0.07$). Interestingly, the incidence of clinically overt heart failure was low in our patient population, both in patients with and in patients without hemodialysis-induced regional LV systolic dysfunction. Taken together, it seems that patients with hemodialysis-induced regional LV systolic dysfunction experience a deterioration of regional rather than global LV systolic function over time.

We should be cautious with the interpretation of our findings for several reasons. First, although this is the largest study on the prognostic effect of hemodialysis-induced LV systolic dysfunction, the number of patients is relatively small, especially in the group with hemodialysis-induced regional LV systolic dysfunction. Second, since mortality was highest in the patients who developed hemodialysis-induced regional LV systolic dysfunction it is conceivable that patients with the worst LV function at baseline had the highest mortality rate. This may have led to an underestimation of a deleterious effect of hemodialysis-induced regional LV systolic dysfunction on the evolution of LV function over time. Our study has also several strengths. First, this is the largest study that evaluated the association between hemodialysis-induced regional LV systolic dysfunction and outcome including 'pure' cardiac events. Second, we showed for the first time that the prognostic effect of hemodialysis-induced regional LV systolic dysfunction is independent of various possible confounders, including inflammatory markers. Third, we used routine and clinically easily applicable echocardiographic methods to evaluate global and regional LV systolic function; a design that is easily reproducible in future studies.

In conclusion, hemodialysis-induced regional LV systolic dysfunction is an independent risk factor for all-cause mortality and cardiac events. Ischemic heart disease rather than cardiac arrhythmias and symptomatic heart failure was the dominant type of cardiac events in these patients. Hemodialysis-induced regional LV systolic dysfunction was not associated with a global change in systolic dysfunction over one-year but tended to be associated with progression of regional LV dysfunction.

Acknowledgements

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Disclosures

None.

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Supplementary table 1 Prognostic effects of hemodialysis-induced regional LV dysfunction on all-cause mortality, cardiac events, and the combined outcome of mortality and cardiac events during a follow-up period of 2 years: adjustment for inflammatory markers.

	HR	CI	P value
All-cause Mortality			
Model 1: Crude model	3.09	1.29-7.43	0.01
Model 2: age and gender	2.52	1.03-6.15	0.04
Model 3: age, gender, dialysis vintage, cardiovascular history, diabetes, ultrafiltration volume, LVMI, and predialysis WMSI	3.80	1.26-11.41	0.02
Model 4: model 2 + CRP	3.41	0.85-13.64	0.08
Model 5: model 2 + pentraxin-3	3.83	1.14-12.84	0.03
Model 6: model 2 + TNF-α	5.01	1.56-16.54	0.008
Model 7: model 2 + IL-6	2.46	0.77-7.82	0.13
Model 8: model 2 + IL-10	3.72	1.19-11.60	0.02
Model 9: model 2 + IL-6/IL-10 ratio	3.91	1.26-12.15	0.02
Cardiac events			
Model 1: Crude model	2.01	0.82-4.93	0.13
Model 2: age and gender	1.91	0.76-4.77	0.17
Model 3: age, gender, dialysis vintage, cardiovascular history, diabetes, ultrafiltration volume, LVMI, and predialysis WMSI	3.77	1.05-13.63	0.04
Model 4: model 2 + CRP	2.57	0.59-11.20	0.21
Model 5: model 2 + pentraxin-3	4.41	1.16-16.73	0.03
Model 6: model 2 + TNF-α	3.78	1.04-13.75	0.04
Model 7: model 2 + IL-6	3.04	0.80-11.53	0.10
Model 8: model 2 + IL-10	3.76	1.02-13.88	0.05
Model 9: model 2 + IL-6/IL-10 ratio	3.80	1.04-13.84	0.04
Combined outcome of mortality and cardiac event			
Model 1: Crude model	2.19	1.07-4.47	0.03
Model 2: age and gender	1.89	0.91-3.91	0.09
Model 3: age, gender, dialysis vintage, cardiovascular history, diabetes, ultrafiltration volume, LVMI, and predialysis WMSI	3.02	1.23-7.43	0.02

Abbreviations: HR: Hazard ratio; CI: Confidence interval; LV: left ventricle; LVMI: left ventricular mass index; WMSI: wall motion score index.

Supplementary table 1 Continued.

	HR	CI	P value
Combined outcome of mortality and cardiac event			
Model 4: model 2 + CRP	3.26	1.14-9.35	0.03
Model 5: model 2 + pentraxin-3	3.51	1.36-9.07	0.009
Model 6: model 2 + TNF-α	3.24	1.29-8.17	0.01
Model 7: model 2 + IL-6	2.65	1.02-6.91	0.05
Model 8: model 2 + IL-10	2.98	1.18-7.54	0.02
Model 9: model 2 + IL-6/IL-10 ratio	3.11	1.25-7.77	0.02

Abbreviations: HR: Hazard ratio; CI: Confidence interval; LV: left ventricle; LVMI: left ventricular mass index; WMSI: wall motion score index.

Chapter 8

Summary and General Discussion

Summary and Discussion

Hemodialysis treatment is live saving for millions of patients with end-stage renal disease worldwide, either as a bridge to renal transplantation or as a life-long treatment. Despite major improvements in dialysis treatment over the past decades, mortality rates of dialysis patients are still unacceptably high. This excess mortality and morbidity is explained partly by traditional cardiovascular risk factors and pre-existing cardiac disease before the start of dialysis[1] and non-traditional risk factors such as anemia, inflammation, and malnutrition[2-5]. It is increasingly recognised that adverse effects of the hemodialysis procedure itself may contribute to the elevated cardiovascular morbidity and mortality. It is becoming more and more evident that current hemodialysis practice imposes acute stress on the cardiovascular system[6]. Indeed, hemodynamic instability is one of the most frequent complications of hemodialysis[7]. The hemodialysis procedure is also temporally related to an increased risk of sudden death[8].

By applying positron emission tomography (PET) scanning in hemodialysis patients, we and others demonstrated that hemodialysis sessions may elicit acute reductions in myocardial blood flow[9,10]. In some patients the fall in myocardial blood flow was severe enough to result in reversible left ventricular (LV) systolic dysfunction (hypokinesia/ akinesia), especially in regions with the greatest fall in MBF, indicative of ischemia/ stunning. In patients with ischemic heart disease, stunning is a strong predictor of a dismal prognosis[11]. Likewise, repetitive hemodialysis-induced myocardial ischemia of sufficient intensity to result in LV dysfunction might be a pathogenetic factor in the high cardiovascular morbidity and mortality in hemodialysis patients. Hemodialysis-induced myocardial ischemia may trigger arrhythmias and repetitive ischemia may lead to cumulative LV dysfunction and eventually result in heart failure, a highly prevalent condition in hemodialysis patients[12].

The main objective of the studies presented in this thesis was to describe a detailed picture of the acute effect of current conventional hemodialysis treatment on left ventricular systolic and diastolic function. This knowledge may help to improve hemodialysis treatment and to reduce its adverse effects.

In **chapter 2** we presented a case to illustrate important aspects of hemodialysis-induced left ventricular dysfunction. This patient participated in a previous study on the effect of hemodialysis on myocardial blood flow and left ventricular function[9]. Gated ^{13}N-NH_3 PET scanning before dialysis and during hemodialysis showed a decrease in global myocardial perfusion of 26% at 30 minutes and of 44% at 220 minutes after the start of dialysis compared with baseline. New left ventricular regional wall motion abnormalities (akinesia or hypokinesia) developed in 2 of 17 left ventricular segments at 30 minutes of dialysis and in 8 of 17 left ventricular segments at 220 minutes of dialysis. The decrease in myocardial blood flow was significantly higher in

segments that developed regional wall motion abnormalities than in those with preserved function. Remarkably, a gated adenosine stress ^{13}N-NH^{3} PET study on a non-dialysis day yielded no signs of myocardial ischemia and intact myocardial perfusion reserve. Although the adenosine stress ^{13}N-NH^{3} PET findings were not strongly suggestive of coronary artery disease, the studies performed under dialysis stress were of concern. Therefore, the patient underwent coronary angiography showing severe calcifications in the left and right coronary arteries, with significant stenosis in the midsection of the right coronary artery, which was treated with a stent. This case illustrates that the hemodialysis procedure itself can elicit a pronounced fall in myocardial perfusion and can induce regional left ventricular dysfunction, especially in regions that experienced the greatest fall in myocardial perfusion. Together these abnormalities are highly suggestive of regional myocardial ischemia occurring during hemodialysis. Importantly, these cardiac abnormalities were asymptomatic in this and other patients[9]. This case also suggests that the hemodialysis procedure imposes a specific type of cardiac stress that is not captured by routine adenosine stress testing. Finally, this study shows that the area of hypokinesia/akinesia that developed during dialysis (anterior, septal, and inferior regions) corresponded only partly to the site of the significant stenosis. This may be due to diffuse coronary artery sclerosis in this patient. Alternatively, microcirculatory disease may have contributed to the development of a larger area of hypoperfusion than expected on the basis of the coronary lesions. McIntyre et al have shown that hemodialysis may induce segmental myocardial hypoperfusion with matching left ventricular systolic dysfunction even in the absence of significant coronary lesions[10].

In **chapter 3** we evaluated the prognostic effect of pre- and postdialysis levels and an intradialytic increase in cardiac troponin I (cTnI), a highly specific myocardial damage marker, using a high-sensitive assay in 90 patients on maintenance hemodialysis. Predialysis cTnI was elevated in 34% of patients. cTnI increased significantly during dialysis and the rise in cTnI had a trend to be associated with longer dialysis vintage. Whereas predialysis cTnI levels were not significantly associated with outcome, a greater intradialysis rise in cTnI was associated with a significantly higher incidence of cardiovascular events, also after correction for age, gender, dialysis vintage, previous cardiovascular events, and predialysis cTnI levels. These findings suggest that hemodialysis may cause myocardial injury. An intradialysis rise in cTnI may help identify patients who are susceptible for the hemodynamic stress of hemodialysis.

In **chapter 4 and 5** we evaluated in detail the effect of hemodialysis on LV function, using serial echocardiographic measurements before, during, and after dialysis. In chapter 4 we showed that about one-quarter of patients developed regional LV systolic dysfunction during dialysis, defined as an increase in wall motion score

(WMS) in two or more segments during/after dialysis. This finding was in line with earlier observations that hemodialysis may acutely induce regional LV systolic dysfunction in a substantial proportion of patients[9,10,13,14], although the proportion of patients that developed hemodialysis-induced regional LV systolic dysfunction in our study was lower than in previous reports[14]. This discrepancy may be explained by differences in patient populations studied and by differences in the methods used to evaluate regional systolic dysfunction of the left ventricle. Recently, Dubin et al[15] using the same method for evaluating LV dysfunction as we did (wall motion score index) reported a similar percentage of patients (26%) with worsening regional LV function during dialysis. Remarkably, in a considerable proportion of patients hemodialysis-induced regional LV systolic dysfunction occurred already early (after one hour) during hemodialysis, when the change in blood volume is known to be marginal[16]. In search of factors that are associated with or are causally related to the development of hemodialysis-induced regional left ventricular dysfunction, we compared various aspects of the hemodialysis treatment between patients who did and those who did not develop left ventricular dysfunction during hemodialysis. Importantly, we did not find any difference in various volume parameters, like ultrafiltration volume, ultrafiltration rate and the course of blood volume between patients with and those without hemodialysis-induced regional left ventricular systolic dysfunction. Therefore, we concluded that volume changes are not the dominant factor in the pathophysiology of hemodialysis-induced regional LV systolic function. This contrasts with findings in a previous study by Burton et al who found a significant association between the ultrafiltration volume and the development of hemodialysis-induced regional left ventricular abnormalities[14]. In a previous study we observed that the reduction in myocardial blood flow occurred early (within 30 minutes after the start of dialysis) during hemodialysis, even in the absence of ultrafiltration[9]. In that study there was also no significant association between total ultrafiltration volume and the change in myocardial blood flow during hemodialysis. In search of patient-related factors that are associated with hemodialysis-induced regional left ventricular dysfunction, we found that this entity associated with male sex, higher LV mass index, and pre-existent (before dialysis) LV dysfunction. It has already been shown that a higher LV mass is associated with a relative reduction in capillary density (myocyte–capillary mismatch)[17], which in combination with myocardial hypoperfusion may contribute to the development of ischemia. The association of a worse predialysis LV function in patients developing regional left ventricular dysfunction during the subsequent dialysis session may either indicate that patients with impaired predialysis systolic function are more susceptible to the cardiac stress induced by the hemodialysis procedure or that repetitive hemodialysis-induced myocardial hypoperfusion (myocardial stunning) has resulted in a deterioration of LV function over time. An interesting finding in this study was that hemodialysis-induced regional LV systolic

dysfunction was independently associated with higher mortality after a mean of 1.5 years follow-up. It was earlier shown that 1-year mortality was higher among patients with myocardial stunning during hemodialysis[14]. In our study, the prognostic impact of hemodialysis-induced regional LV systolic dysfunction was independent of age, gender, cardiovascular history, dialysis vintage, diabetes, LV mass index, and predialysis WMSI.

In **chapter 5** we focused on the acute effect of hemodialysis on another aspect of LV function, namely the relaxation of the left ventricle, also named diastolic function. In contrast to previous studies, we assessed diastolic function not only before and after the dialysis session but also early and late during hemodialysis and related diastolic function parameters to changes in blood volume and B-type natriuretic peptide (BNP) levels. Similar to previous reports[18-20], we also observed that diastolic function worsened from pre- to postdialysis. Additionally, we showed that worsening of diastolic function during hemodialysis was even more pronounced than is captured when only pre- and postdialysis echocardiography are performed since partial recovery of diastolic function was observed at the 30 minute postdialysis echocardiography. Since diastolic echocardiographic parameters are known to be dependent on pre-load volume, most groups concluded that the worsening of diastolic function form pre- to postdialysis is explained by hypovolemia induced by ultrafiltration[19,20]. For our study, we focused on the change of two important diastolic parameters, namely mitral valve inflow and tissue Doppler velocities, the former being known as volume dependent [18] and the latter as less volume-dependent[21]. Both parameters decreased significantly during dialysis, but, remarkably, the steepest change for both parameters occurred in the first hour of hemodialysis when ultrafiltration-induced hypovolumia was only minimal. Furthermore, although the change in mitral valve inflow was significantly associated with the change in blood volume both early and late during dialysis, tissue Doppler-derived velocity was not at all associated with either the change in blood volume or ultrafiltration volume at both time points during hemodialysis. The course of Doppler-derived velocity values did not mirror the change in blood volume. These results challenge the importance of blood volume changes during hemodialysis as the dominant factor for the intradialysis deterioration of diastolic parameters. Notably, we can not fully exclude that hypovolemia contributed to the worsening of diastolic parameters because of the limitations that are inherent to the measurement of relative blood volume changes, but at the same time we believe that our results raise the intriguing possibility that non-volume related mechanisms are involved in the early decrease in tissue Doppler early diastolic velocity. First, LVH may contribute to diastolic dysfunction because it opposes LV diastolic filling[22]. Second, reductions in blood pressure[23] and increases in heart rate[24] may affect diastolic filling. Third, changes in plasma calcium and magnesium concentrations may influence LV relaxation[25,26]. Fourth, hemodialysis-induced

myocardial ischemia may cause impaired LV relaxation and thus diastolic dysfunction during hemodialysis may just represent an aspect of cardiac stress caused by hemodialysis in addition to systolic dysfunction. Likewise, in a recent editorial that accompanied our publication, Selby et al[27] implied hemodynamic factors, hemodialysis-induced subclinical ischemia, and an increase in ionised calcium levels during hemodialysis as possible factors affecting diastolic function during dialysis session.

In **chapter 6**, we explored the association between hemodialysis-induced regional systolic left ventricular dysfunction and inflammation. Inflammation could have a pathophysiological role in this entity, e.g. by a cardiodepressive effect of inflammatory cytokines on cardiac function and/or a negative effect of inflammation on endothelial function[28]. Intact endothelial function is important in the regulation of microcirculatory blood flow especially under hemodynamic stress conditions like hemodialysis treatment. Therefore, in **chapter 6**, we related the development of hemodialysis-induced regional LV systolic dysfunction to various markers of inflammation and endothelial function. We found that predialysis levels of the acute phase proteins hsCRP and PTX3 as well as the pro-inflammatory cytokine IL-6 and the ratio between IL-6 and the anti-inflammatory cytokine IL-10 were significantly higher in patients who subsequently developed hemodialysis-induced regional LV systolic dysfunction than those who did not. hsCRP and IL-6/IL-10 ratio showed a dose-response relation with higher levels in patients who developed a greater number of abnormal segments during hemodialysis. We, therefore, concluded that there is a significant association between regional LV systolic dysfunction during hemodialysis and systemic inflammation. The nature of this association remains speculative. Inflammation could have a pathophysiological role in the development of LV systolic dysfunction during hemodialysis, e.g. by increasing the susceptibility for cardiac ischemia through a negative effect of inflammation on endothelial function of the myocardial microcirculation[29] and/or by cardiodepressive effects of pro-inflammatory cytokines[30]. Alternatively, higher concentrations of inflammatory markers may represent a higher atherosclerotic burden in these patients[31]. It could also reflect an underlying endotoxemia, which has been shown to be associated with hemodialysis-induced myocardial stunning[32]. Finally, chronic inflammation can be the consequence rather than the cause of repetitive myocardial ischemia since repetitive ischemia-reperfusion of the heart may lead to increased inflammatory cytokine levels[33]. This may even initiate a vicious cycle in which elevated concentrations of pro-inflammatory cytokines may further impair cardiac perfusion and function. Importantly, we observed similar courses for inflammatory and bioincompatibility markers in patients with and in those without hemodialysis-induced regional LV systolic dysfunction. This suggests that acute inflammatory and bioincompatibility reactions as a result of the hemodialysis procedure itself were not responsible for the development of regional LV systolic dysfunction during hemodialysis.

In **chapter 7** we studied in detail the effect of hemodialysis-induced regional LV systolic dysfunction on patient outcome and the development of systolic left ventricular function. We found that during a one-year follow-up deterioration of regional but not global systolic function was more pronounced in patients with than in those without hemodialysis-induced regional LV systolic dysfunction. Patients with hemodialysis-induced regional LV systolic dysfunction experienced independently higher all-cause mortality rates, cardiac events, and combined outcome of all-cause mortality and cardiac events after two years, after adjustment for cardiovascular cofounders and inflammatory status.

In conclusion, this thesis describes current conventional hemodialysis as a procedure that has an acute deleterious effect on systolic and diastolic left ventricular function. The development of regional left ventricular systolic dysfunction during hemodialysis is associated with higher all-cause mortality and cardiac events. The occurrence of regional systolic dysfunction is linked with chronic inflammation.

Several limitations of the studies presented in this thesis deserve discussion. In **chapter 3** we could not correct the intradialysis change in cTnI levels for hemoconcentration. However, the rise in cTnI levels was greater than could be expected by hemoconentration alone and there was no association between the change in cTnI levels and ultrafiltration volume. In **chapter 4** we acknowledge the lack of angiographic evaluation of coronary arteries and, therefore, the inability to correlate the development of hemodialysis-induced regional left ventricular dysfunction with underlying coronary atherosclerotic lesions. Furthermore, we used a non-validated definition for regional left ventricular systolic dysfunction, since a validated or accepted definition for this entity is lacking. Notably, the use of different definitions will affect the prevalence and, possibly, also the prognostic impact of this entity. In **chapter 5** we acknowledged that changes in relative blood volume may not mirror changes in absolute and central blood volume and may not capture the hypovolemic effect of the transition of blood to the extracorporal system. Another limitation of this study was the lack of measurement of left atrial volume, as a validated parameter of diastolic function. In **chapter 6**, the lack of angiographic studies made it impossible to relate the markers of inflammation to the extent of atherosclerosis. In addition, endotoxin levels were not measured as a potential factor explaining the higher concentrations of inflammatory markers in patients with hemodialysis-induced regional LV systolic dysfunction.

Future perspective

In this thesis we aimed to evaluate cardiac function and associated factors during hemodialysis. We conclude that regional systolic and diastolic function is impaired during dialysis and the impairment of regional systolic function is associated with

worse outcome. Cardiac dysfunction seems not to be only explained by reduction in blood volume during dialysis and other mechanisms such as inflammation appear to be associated with occurrence of cardiac dysfunction during dialysis. Focusing on these less known adverse effects of hemodialysis and elucidating their pathophysiological mechanisms may help to improve dialysis treatment and, possibly, improve the quality of lives of the many patients who are dependent on this treatment. Future studies should therefore further explore the exact mechanisms of the occurrence of hemodialysis-induced regional LV dysfunction by first validation of a common method of evaluation of cardiac dysfunction during dialysis and then evaluation of patient and dialysis-specific factors including exact blood volume change in larger and more homogeneous patient population. The pathophysiological association between systemic inflammation and hemodialysis-induced regional LV dysfunction should also be explored in more detail in larger comparative studies. Moreover, there is still more to be known about the interaction between diastolic and systolic dysfunction during hemodialysis. Likewise, the relative contribution of ultrafiltration and dialysis to the fall in myocardial blood flow and the development of RWMA and/or diastolic dysfunction should be studied in detail, by using other imaging method such as PET scan that are capable of measuring myocardial perfusion and to some extent systolic and diastolic LV function or the combination of PET scan and echocardiography to make the evaluation of LV function complete.

The findings of the present thesis and related research may provide a rational basis for intervention studies with the aim to prevent the development and/or consequences of hemodialysis-induced regional LV dysfunction. It has previously been shown that intensified dialysis schedules like frequent (nocturnal) hemodialysis regimes are associated with significant reduction in occurrence of dialysis-induced myocardial stunning[34]. More research is needed to definitely establish these proposed beneficial effects of frequent dialysis regimes on LV function and to elucidate the nature of its possible beneficial effect, to further establish cardiac risks and benefits of hemodialysis. Possible other candidates for prevention are beta-blockers (anti-ischemic action) or ACE-i/ARBs (anti-inflammatory effect and reduction of sympathetic overactivity).

With this prospective, it is clear that we are just in the beginning of a way toward exploration of adverse effects of hemodialysis and there is a still much more to perform in order to optimize this life-saving treatment for hemodialysis patients and minimize the adverse effects so that these patients would also lead, at least, a near to normal life after losing their renal function.

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Nederlandse samenvatting

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Hemodialyse behandeling is wereldwijd levensreddend voor miljoenen patiënten met eindstadium nierziekte, hetzij als een brug naar niertransplantatie of als een levenslange behandeling. Ondanks belangrijke verbeteringen in de dialysebehandeling in de afgelopen decennia, is de sterfte van dialysepatiënten nog steeds veel hoger dan bij personen met een normale nierfunctie. Deze verhoogde mortaliteit wordt deels verklaard door traditionele risicofactoren en reeds bestaande hartaandoeningen voor de start van dialyse en deels door minder bekende risicofactoren zoals bloedarmoede, chronische ontsteking en ondervoeding. Het wordt steeds meer erkend dat ook de nadelige gevolgen van de hemodialyse behandeling zelf kunnen bijdragen aan het vaker voorkomen van hartziektes en sterfte. De huidige conventionele hemodialyse behandeling gaat gepaard met acute stress op het cardiovasculaire systeem. Hemodynamische instabiliteit is één van de meest voorkomende complicaties van hemodialyse. De hemodialyse behandeling is in tijd ook gerelateerd aan een verhoogd risico op plots overlijden.

Met het gebruik van positron emissie tomografie (PET) scan tijdens hemodialyse hebben wij en anderen eerder aangetoond dat een hemodialyse behandeling een acute vermindering in bloeddoorstroming van het hart kan veroorzaken. Bij sommige patiënten ging de daling van de bloeddoorstroming van de hartspier gepaard met reversibele (omkeerbare) wandbewegingsstoornissen van een deel van de linker hartkamer, vooral in regio's waar de grootste daling van de bloeddoorstroming optrad. Dit fenomeen noemen we regionale hemodialyse geïnduceerde linker kamer disfunctie. De combinatie van wandbewegingsstoornissen en verminderde doorbloeding doet vermoeden dat er sprake is van tijdelijk tekort van zuurstofaanbod (ischemie) aan de hartspier. Bij patiënten met een hartziekte is reversibele linker kamer disfunctie een sterke voorspeller van een slechte prognose. De bij herhaling tijdens hemodialyse optredende linker kamer disfunctie/ ischemie kan één van de factoren zijn die bijdraagt aan het verhoogd voorkomen van hartziektes en sterfte bij hemodialyse patiënten. Hemodialyse geïnduceerde ischemie van het hart kan leiden tot hartritmestoornissen en herhaald optredende ischemie zou kunnen leiden tot progressieve linker kamer disfunctie en uiteindelijk kunnen resulteren in hartfalen. Hartfalen is een vaak voorkomende aandoening bij hemodialyse patiënten.

Het belangrijkste doel van de studies in dit proefschrift is om een gedetailleerd beeld van het acute effect van de huidige conventionele hemodialyse behandeling op de linker kamer functie en relaxatie te geven. Deze kennis kan helpen om de hemodialyse behandeling te verbeteren en de bijwerkingen te verminderen.

In hoofdstuk 2 presenteren we een casus om een aantal belangrijke aspecten van hemodialyse geïnduceerde linker kamer disfunctie te illustreren. Deze patiënt heeft deelgenomen aan een eerdere studie over het effect van hemodialyse op de bloeddoorstroming van het hart en linker kamer functie. PET scans werden verricht voor en tijdens hemodialyse, en toonden een daling van de bloeddoorstroming van de linker hartkamer tijdens dialyse. Nieuwe wandbewegingsstoornissen van de linker hartkamer ontwikkelden zich in 2 van 17 linker kamer segmenten op 30 minuten na de start van de dialyse en in 8 van 17 linker ventrikel segmenten op 220 minuten na start van de dialyse. De daling van de bloeddoorstroming van het hart was significant hoger in de segmenten, die regionale disfunctie ontwikkelden, dan in de segmenten met bewaarde functie. Opmerkelijk was dat een (adenosine) stress PET studie op een niet-dialyse geen tekenen van ischemie en een intacte bloeddoorstroming van het hart liet zien. Hoewel de stress PET bevindingen niet sterk suggestief waren voor kransslagaderziekte, waren de PET bevindingen tijdens hemodialyse zorgwekkend. Daarom heeft de patiënt een hartcatheterisatie ondergegaan die ernstige verkalkingen in de linker en rechter kransslagaders toonde, met een significante vernauwing in de rechter kransslagader. De vernauwing werd gedotterd en er werd een stent geplaatst. Deze casus illustreert dat de hemodialyse procedure zelf een uitgesproken daling kan uitlokken in de bloeddoorstroming van het hart en regionale linker kamer disfunctie kan veroorzaken. Samen zijn deze afwijkingen zeer suggestief voor regionale ischemie tijdens hemodialyse. Belangrijk is dat deze cardiale afwijkingen tijdens hemodialyse asymptomatisch zijn. Tevens suggereert dit casus dat hemodialyse een specifiek type van cardiale stress veroorzaakt die niet wordt ontdekt door een routine stress onderzoek van het hart met adenosine. In deze casus was er sprake van een significante coronairafwijking in de rechter kransslagader. De wandbewegingsstoornissen, die tijdens dialyse ontstonden, waren echter uitgebreider dan het gebied dat door de rechter kransslagader van bloed wordt voorzien. Eerder heeft een andere onderzoeksgroep laten zien dat de hemodialyse geïnduceerde linker kamer disfunctie ook op kan treden zonder dat er sprake is van kransslagaderafwijkingen.

In hoofdstuk 3 hebben we de prognostische waarde onderzocht van zowel voor als na de dialyse bepaalde bloedspiegels van troponine I bij 90 hemodialyse patiënten. Troponine I is een zeer specifieke merker van spierschade van het hart en werd gemeten met behulp van een zeer gevoelige methode. Voor dialyse was de troponine I spiegel verhoogd bij 34% van de patiënten. Tijdens de dialyse nam de troponine I spiegel aanzienlijk toe en een stijging van de troponine I spiegel was geassocieerd met het vaker voorkomen van hartziektes. Deze bevindingen suggereren dat hemodialyse spierschade van het hart kan veroorzaken. Een stijging van troponine I tijdens dialyse kan helpen bij het identificeren van patiënten waarvan het hart gevoelig is voor de invloed van de hemodynamische stress van hemodialyse.

In hoofdstuk 4 en 5 evalueerden we in detail de effecten van hemodialyse op de linker kamer functie met seriële echocardiografische metingen voor, tijdens en na dialyse. In hoofdstuk 4 laten we zien dat ongeveer een kwart van de patiënten regionale linker kamer disfunctie ontwikkelde tijdens de dialyse. Deze bevinding is in lijn met eerdere studies die lieten zien dat hemodialyse acute regionale linker kamer disfunctie in een aanzienlijk deel van patiënten kan veroorzaken. Het percentage patiënten dat hemodialyse geïnduceerde regionale linker kamer disfunctie ontwikkelde was in ons onderzoek echter lager dan in een eerdere publicatie (Burton en anderen). Dit verschil kan worden verklaard door verschillen in de karakteristieken van de bestudeerde patiëntengroep en door verschillen in de gebruikte methoden om regionale linker kamer disfunctie van het hart te evalueren. In een studie met een vergelijkbare methode als onze studie voor het evalueren van linker kamer disfunctie, hebben Dubin en anderen onlangs een vergelijkbaar percentage patiënten gerapporteerd die regionale linker kamer disfunctie tijdens dialyse ontwikkelde. In ons onderzoek trad hemodialyse geïnduceerde regionale linker kamer disfunctie bij een aanzienlijk deel van de patiënten reeds vroeg (na een uur) tijdens de hemodialyse op. Op zoek naar factoren die geassocieerd zijn of een causaal verband hebben met de ontwikkeling van hemodialyse geïnduceerde regionale linker kamer disfunctie, vergeleken we de verschillende aspecten van de hemodialyse behandeling tussen patiënten die wel en degenen die geen linker kamer disfunctie tijdens hemodialyse ontwikkelden. Belangrijk was dat we geen verschil vonden in verschillende volume parameters zoals ultrafiltratie volume, ultrafiltratie snelheid en het beloop van het bloedvolume tussen patiënten met en zonder hemodialyse geïnduceerde regionale linker kamer disfunctie. Daarom hebben wij geconcludeerd dat volume veranderingen tijdens hemodialyse niet de hoofdoorzaak zijn van hemodialyse geïnduceerde regionale linker kamer disfunctie. Dit is in tegenstelling tot de bevindingen van een eerder onderzoek door Burton en anderen die een significante associatie tussen het ultrafiltratie volume en de ontwikkeling van regionale linker kamer afwijkingen tijdens dialyse vonden. In ons eerdere PET onderzoek hebben we gevonden dat de bloeddoorstroming van het hart vroeg tijdens de hemodialyse (binnen 30 minuten na de start van dialyse) en voor de start van ultrafiltratie significant afneemt. Tevens was er geen significant verband tussen het totale ultrafiltratie volume en de verandering van de bloeddoorstroming van het hart tijdens hemodialyse. Van de patiëntgebonden factoren waren mannelijk geslacht, hartmassa, en reeds voor dialyse aanwezige linker kamer disfunctie, geassocieerd met het optreden van hemodialyse geïnduceerde regionale linker kamer disfunctie. Het is bekend dat een hogere hartmassa (linker kamer hypertrofie) geassocieerd is met een relatieve vermindering van de verhouding tussen bloedvaten en spiermassa die in combinatie met een verminderde bloeddoorstroming kan bijdragen aan de ontwikkeling van ischemie. De associatie van een reeds voor de dialyse bestaande linker kamer disfunctie met het ontwikkelen van

regionale linker kamer disfunctie tijdens dialyse kan aangeven dat deze patiënten vatbaarder zijn voor de cardiale stress veroorzaakt door de hemodialyse. Een alternatieve verklaring is dat bij herhaling optredende hemodialyse geïnduceerde daling van de bloeddoorstroming van het hart in de loop van de tijd een verslechtering van de linker kamer functie veroorzaakt. Het optreden van hemodialyse geïnduceerde regionale linker kamer disfunctie was onafhankelijk geassocieerd met een hogere sterfte tijdens een periode van gemiddeld 1,5 jaar. Deze bevinding was conform het eerdere onderzoek van Burton en anderen. In ons onderzoek was het prognostische effect van hemodialyse geïnduceerde regionale linker kamer disfunctie onafhankelijk van andere factoren die sterfte kunnen beïnvloeden.

In hoofdstuk 5 hebben we ons gericht op het acute effect van hemodialyse op een ander aspect van de linker kamer functie, namelijk de relaxatie van de linker ventrikel, of wel diastolische functie. In tegenstelling tot eerdere studies hebben we diastolische functie niet alleen beoordeeld voor en na de dialyse behandeling, maar ook tijdens hemodialyse. We hebben daarbij ook de verandering van de diastolische functie gerelateerd aan veranderingen van het bloedvolume tijdens de dialyse. Net als gevonden is in eerdere onderzoeken, constateerden we dat de diastolische functie slechter was na de dialyse vergeleken met voor de hemodialyse. Daarnaast bleek dat de diastolische functie tijdens hemodialyse nog veel meer verslechterde dan werd gedacht op grond van de vergelijking van de diastolische functie voor en na de dialysebehandeling. Dit komt door een gedeeltelijk herstel van de diastolische functie in de 30 minuten na afloop van de dialysebehandeling. Het is bekend dat diastolische echocardiografische parameters afhankelijk zijn van het zogenaamde pre-load volume (volumebelasting van het hart). Daarom hebben de meeste onderzoeksgroepen eerder geconcludeerd dat de verslechtering van de diastolische functie na dialyse verklaard werd door een verminderd bloedvolume, veroorzaakt door ultrafiltratie. Voor onze studie hebben we ons gericht op de verandering van twee belangrijke diastolische parameters, waarvan één parameter (e') minder afhankelijk is van de volumestatus. Beide parameters daalden aanzienlijk tijdens de dialyse, maar opvallend was dat de grootse verandering van beide parameters zich voordeed in het eerste uur van hemodialyse, wanneer de daling van het bloedvolume door ultrafiltratie slechts minimaal was. Daarnaast was de verandering van de diastolische parameter e' niet gecorreleerd met de verandering in bloedvolume. Tevens kwam het beloop van deze waarde niet overeen met de verandering in het bloedvolume. Deze resultaten betwisten het belang van bloedvolume veranderingen tijdens hemodialyse als de belangrijkste oorzaak voor de verslechtering van diastolische parameters tijdens dialyse. We kunnen echter niet geheel uitsluiten dat de daling in bloedvolume bijgedragen heeft tot de verslechtering van diastolische parameters door de beperkingen die inherent zijn aan de meting van relatieve bloedvolume

veranderingen. Tegelijkertijd suggereren onze resultaten dat niet-volume gerelateerde mechanismen betrokken zijn bij de vroege achteruitgang van de diastolische functie. Mogelijke mechanismen zijn 1. Hypertrofie (verdikking) van de linker kamer met een vertraagde vulling; 2. daling van de bloeddruk en een toename van de hartslag waardoor de diastolische vulling wordt beïnvloed; 3. veranderingen in de bloedspiegels van calcium en magnesium met beïnvloeding van de relaxatie van de linker kamer; 4. Hemodialyse geïnduceerde ischemie van de linker kamer kan de relaxatie van de linker kamer vertragen. Het is dus mogelijk dat de verslechtering van de diastolische functie tijdens hemodialyse een uiting is van door hemodialyse veroorzaakte cardiale stress.

In hoofdstuk 6 onderzochten we het verband tussen hemodialyse geïnduceerde regionale linker ventrikel disfunctie en ontsteking. Ontsteking kan een pathofysiologische rol hebben, bijvoorbeeld door een remmend effect van ontstekingsmediatoren op de hartfunctie en/ of door een negatief effect van ontsteking op de functie van endotheelcellen, de binnenbekleding van bloedvaten. Intacte functie van de endotheelcellen is belangrijk voor de regulatie van de bloeddoorstroming in het bijzonder bij omstandigheden met hemodynamische stress, zoals tijdens een hemodialyse behandeling. In hoofdstuk 6 hebben we daarom het verband onderzocht tussen de ontwikkeling van hemodialyse geïnduceerde regionale linker kamer disfunctie en verschillende merkers van ontsteking en endotheelfunctie. We vonden dat het niveau van de acute fase ontstekingsmerkers voor de dialyse significant hoger waren bij patiënten die vervolgens hemodialyse geïnduceerde regionale linker kamer disfunctie ontwikkelden. Twee van die merkers hadden een hoger niveau naarmate een groter aantal segmenten wandbewegingsstoornissen ontwikkelde tijdens hemodialyse. Concluderend blijkt er een significant verband te zijn tussen hemodialyse geïnduceerde regionale linker kamer disfunctie en systemische ontsteking. De aard van deze associatie blijft speculatief. Ontsteking zou een pathofysiologische rol in de ontwikkeling van linker kamer disfunctie tijdens hemodialyse kunnen spelen, bijvoorbeeld door het verhogen van de gevoeligheid voor cardiale ischemie door een negatief effect van ontsteking op de functie van de endotheelcellen van het hart en/of door remmende effecten van ontstekingsmediatoren op het hart zelf. Een alternatieve verklaring is dat hogere concentraties van ontstekingsfactoren een reflectie zijn van ernstigere vaatverkalkingen bij deze patiënten. Er kan ook sprake zijn van verhoogde bloedspiegels van bacterietoxinen (endotoxinen), waarvan eerder is aangetoond dat het geassocieerd is met hemodialyse geïnduceerde linker kamer disfunctie. Tenslotte is het ook mogelijk dat de chronische ontsteking niet de oorzaak maar een gevolg is van herhaalde myocardiale ischemie, aangezien herhaald zuurstoftekort van het hart kan leiden tot verhoogde ontstekingsmerkers. Dit kan zelfs leiden tot een vicieuze cirkel, waarbij een hoge concentratie van ontstekingsmerkers de cardiale doorbloeding en functie verder kan belemmeren. Het beloop van de ontstekingsmerkers tijdens

hemodialyse was overigens vergelijkbaar bij patiënten met en zonder hemodialyse geïnduceerde regionale linker kamer disfunctie. Dit suggereert dat een acute ontstekingsreactie als gevolg van de hemodialysebehandeling zelf niet verantwoordelijk is voor de ontwikkeling van regionale linker kamer disfunctie tijdens hemodialyse.

In hoofdstuk 7 bestudeerden we in detail de invloed van hemodialyse geïnduceerde regionale linker kamer disfunctie op de prognose van patiënten en de ontwikkeling van de linker kamer functie. We vonden dat gedurende één jaar follow-up de verslechtering van de regionale linker kamer functie meer uitgesproken was bij patiënten met in vergelijking met patiënten zonder hemodialyse geïnduceerde regionale linker kamer disfunctie. Hemodialyse geïnduceerde regionale linker kamer disfunctie is een onafhankelijke risicofactor voor zowel een hogere mortaliteit als cardiale ziektes gedurende een observatieperiode van twee jaar.

Samengevat, laten de onderzoeken die beschreven staan in dit proefschrift zien dat de huidige conventionele hemodialyse procedure acute schadelijke effecten heeft op de linker kamer functie en relaxatie. De ontwikkeling van regionale linker kamer disfunctie tijdens hemodialyse is geassocieerd met een hogere mortaliteit en vaker voorkomen van cardiale problemen. Het optreden van regionale linker kamer disfunctie is verbonden met chronische ontsteking.

Een aantal beperkingen van de studies in dit proefschrift verdienen discussie. In hoofdstuk 3 konden we de verandering van de bloedspiegels van troponine I tijdens de hemodialyse niet corrigeren voor de daling van het bloedvolume door ultrafiltratie (hemoconcentratie). De stijging van de troponine I spiegels was echter groter dan door hemoconcentratie te verwachten was. Tevens was er geen verband tussen de verandering in troponine I spiegels en het ultrafiltratie volume. Een beperking van het onderzoek beschreven in hoofdstuk 4 is het gebrek aan evaluatie van de kransslagaders door een hartcatheterisatie. Daardoor was het niet mogelijk om de ontwikkeling van hemodialyse geïnduceerde regionale linker kamer disfunctie te relateren aan eventuele onderliggende vernauwingen van de kransslagaders. Verder gebruikten we een niet gevalideerde definitie voor regionale linker kamer disfunctie, omdat een gevalideerde of aanvaarde definitie voor deze afwijking ontbreekt. Het gebruik van alternatieve definities beïnvloed waarschijnlijk de prevalentie en mogelijk ook het prognostische effect van deze afwijking. In hoofdstuk 5 erkennen we dat veranderingen in de relatieve bloedvolume niet altijd vergelijkbare veranderingen van het absolute en centrale bloedvolume weerspiegelen en niet het hypovolemische effect van de overgang van het bloed naar de dialyselijnen en de kunstnier vastleggen. Een andere beperking van dit onderzoek was het ontbreken van gegevens over het volume van de linker boezem. Dit is een gevalideerde parameter van de relaxatie van linker kamer.

In hoofdstuk 6 maakte het ontbreken van hartcatheterisatie bij de bestudeerde patiënten het onmogelijk om ontstekingsmerkers te correleren aan de mate van vaatverkalkingen in de kransslagaders. Bovendien hebben we geen bloedspiegels van endotoxinen gemeten als mogelijke verklaring voor de hogere concentraties van ontstekingsmerkers bij patiënten met hemodialyse geïnduceerde regionale linker kamer disfunctie.

Toekomstperspectief

In dit proefschrift hebben we de hartfunctie en geassocieerde factoren tijdens hemodialyse geëvalueerd. We concluderen dat hemodialyse bij een aanzienlijk deel van patiënten een acute verslechtering geeft van de regionale linker kamer functie en de relaxatie van de linker kamer. De verslechtering van regionale linker kamer functie is geassocieerd met een slechtere uitkomst. Cardiale disfunctie lijkt niet alleen te verklaren te zijn door een afname van het bloedvolume tijdens hemodialyse en andere mechanismen, zoals ontsteking, blijken geassocieerd te zijn met het optreden van cardiale disfunctie tijdens dialyse. Focussen op deze minder bekende negatieve effecten van hemodialyse en het ophelderen van hun mechanismen kan helpen om de dialysebehandeling te verbeteren en eventueel de kwaliteit van leven van de vele patiënten te verbeteren die afhankelijk zijn van deze behandeling. Toekomstige studies zouden daarom verder de exacte mechanismen van het optreden van hemodialyse geïnduceerde regionale linker kamer disfunctie moeten onderzoeken. Het mechanisme van de associatie tussen ontsteking en hemodialyse geïnduceerde regionale linker kamer disfunctie moet ook in meer detail worden onderzocht in grotere studies. Bovendien is er nog weinig bekend over de interactie tussen linker kamer functie en relaxatie tijdens hemodialyse. Evenzo moet de relatieve bijdrage van ultrafiltratie enerzijds en dialyse anderzijds op de daling van cardiale bloeddoorstroom en de ontwikkeling van regionale linker kamer disfunctie en relaxatie worden bestudeerd, bijvoorbeeld met andere beeldvormende werkwijze zoals PET scan of de combinatie van PET scan en echocardiografie waardoor de bloeddoorstroming van het hart en de linker kamer functie en relaxatie completer geëvalueerd kunnen worden.

De bevindingen van dit proefschrift, en het vervolgonderzoek kan een rationele basis vormen voor interventie studies met als doel de ontwikkeling en/of de gevolgen van hemodialyse geïnduceerde regionale linker kamer disfunctie te voorkomen. Eerder is aangetoond dat intensievere hemodialyse schema's zoals frequente (nachtelijke) hemodialyse geassocieerd zijn met het minder vaak optreden van dialyse geïnduceerde linker kamer disfunctie. Meer onderzoek is nodig om deze voorgestelde gunstige

effecten van frequente dialyse regimes op de linker kamer functie te bevestigen en de aard van de mogelijk gunstige werking te achterhalen.

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Curriculum Vitae

Dankwoord

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Solmaz, Groningen 2014

About the author

Solmaz Assa was born on 13 may 1981 in Tehran. She finished her high school at the age of 18 years. Thereafter she attended the national university exam and was accepted for the medical education at the Tehran University of Medical sciences. She finished her medical courses and internship in different hospitals in Tehran and was graduated in July 2008. During her medical education she participated in different research programs in the departments of pharmacology, plastic surgery and gastroenterology, which eventually resulted into several pubmed publications. Shortly before her graduation she attended the student's congress ISCOMS in Groningen. In a speed-dating meeting she got acquaintance with the nephrology department and became interested to the project of Dr. Casper Franssen about cardial dysfunction in hemodialysis. After returning to Tehran she was informed that this project awarded a grant from the Nierstichting and that she could start her PHD program in November 2008 under supervision of prof. dr. Paul de Jong and prof. dr. Adriaan Voors.

Solmaz presented the results of her PHD research in different national (Dutch nephrology days) and international (American society of nephrology) congresses and this finally ended in the formation of this thesis in 2014.

During her PHD project she became interested in cardiology and decided to continue her future education in this field. For being able to work as a medical doctor in the Netherlands she had to first pass a national assessment for the foreign medical doctors, which she accomplished simultaneously with her PHD program. Thereafter she followed a 6 months internship in the Scheper hospital in Emmen and became registered as a Dutch medical doctor.

Solmaz is currently working as a medical resident (arts-assistant niet in opleiding) at the department of cardiology at the University Medical Centre Groningen.